From: Jeannette Barrett
To: Ivan Shaw
Sent: 7/11/2012 9:00:04 AM
Subject: FW: Kadian information
Attachments: 10-02-18 FDA Warning Letter.pdf; Volume 1.1.pdf

There is a whole lot of a paper NDA in Elizabeth. I am thinking we should meet there on Monday July 23rd and spend at least part of the day going through it. What do you think? It will be easier for you coming from the airport and we can (you) have white castle for dinner. A perfect day.

I will arrange it with Carla.

From: Joann Stavole
Sent: Tuesday, July 10, 2012 4:32 PM
To: Jeannette Barrett
Cc: Jennifer Altier; Nathalie Leitch; Terri Nataline; Carla Hedrick
Subject: Kadian information

Hi Jeannette,

I will not be available for the meeting tomorrow, however I am providing some information to get you started.

I have provided the original warning letter from DDMAC regarding our advertising.

Jennifer stated she will send you the latest labeling with the REMS and the approved new strengths.

Also, I have included volume 1.1 from the NDA. It contains an index of the clinical studies that you may be interested in reviewing.

Most of the Kadian files are still in hard-copy located in Elizabeth so you will need to coordinate with Carla accordingly.

Kind regards,
Joann

Joann Stavole
Director, Regulatory Affairs

Description:
C:\Documents and Settings\JSTAVOLE\App Data\Microsoft\Signatur

Actavis
60 Columbia Rd. Bldg B *t* +1 973-889-6623 @ JSTAVOLE@actavis.com
Morristown , NJ 07960 United States *w* www.actavis.com
Internal VoIP number *t* 125-6623

PLAINTIFFS TRIAL EXHIBIT
P-23057_00001

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF DRUG MARKETING, ADVERTISING, AND COMMUNICATIONS
10903 NEW HAMPSHIRE AVE, BLDG #51
SILVER SPRING, MD 20993

FAX

Date: February 18, 2010

To: **Doug Boothe**
Chief Executive Officer
Actavis US

Fax: **(973) 993-4303**

Phone: **(908) 527-9100**

From: Elaine Hu Cunningham, Pharm.D.,
LCDR, United States Public Health Service
Senior Regulatory Review Officer
Phone: (301) 796-1200
Fax: (301) 847-8444

Subject: **NDA 20-616 / MACMIS #18148**

Pages: **12** (not including cover sheet)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Doug Boothe, Chief Executive Officer
Actavis US
60 Columbia Road, Building B
Morristown, NJ 07960

RE: NDA #20-616
Kadian® (morphine extended-release) Capsules, CII
MACMIS #18148

WARNING LETTER

Dear Mr. Boothe:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a Co-Pay Assistance Program brochure (KAD200901) for Kadian® (morphine extended-release) Capsules, CII (Kadian), submitted by Actavis Elizabeth LLC (Actavis) under cover of Form FDA-2253. DDMAC has also reviewed a PK to PK Comparison Detailer (Comparison Detailer) (KADI8D0231) for Kadian that was originally submitted by Alpharma under cover of Form FDA-2253.[1] The Co-Pay Assistance Program brochure and Comparison Detailer are false or misleading because they omit and minimize the serious risks associated with the drug, broaden and fail to present the limitations to the approved indication of the drug, and present unsubstantiated superiority and effectiveness claims. Therefore, the Co-Pay Assistance Program brochure and Comparison Detailer misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (ii) & (xviii); (e)(7)(i) & (viii). These violations are a concern from a public health perspective because they suggest that the product is safer and more effective than has been demonstrated.

Background

The INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) for Kadian states (emphasis in original):

> KADIAN® Capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time . . . .
>
> **KADIAN® Capsules are NOT intended for use as a prn analgesic.**

[1] As of January 8, 2009, NDA 20-616 has been transferred to Actavis US.

KADIAN® is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. KADIAN® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. . . .

Kadian is associated with a number of serious risks, many of which are potentially fatal. The PI includes the following boxed warning concerning potentially fatal overdosing if Kadian capsules are chewed, crushed, or dissolved, and other serious risks (emphasis in original):

WARNING:
KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

KADIAN® Capsules are NOT for use as a prn analgesic.

KADIAN® 100 mg and 200 mg Capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. KADIAN® CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLE SAUCE. THE PELLETS IN THE CAPSULES ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

The PI states that Kadian is contraindicated in any situation where opioids are contraindicated. This includes patients with respiratory depression in the absence of resuscitative equipment or in unmonitored settings, in patients with acute or severe bronchial asthma or hypercarbia, and in patients who have or are suspected of having paralytic ileus.

The PI includes warnings, in addition to the boxed and bolded warnings, related to the potentially fatal abuse potential of opioids, use by individuals other than the patient for

whom the drug was prescribed, interactions with alcohol and drugs of abuse, impaired respiration, head injury and increased intracranial pressure, hypotensive effect, interactions with other central nervous system (CNS) depressants, gastrointestinal obstruction, and anaphylaxis.

There are a number of precautions associated with Kadian, including the general precautions that it is intended for use in patients who require continuous, around-the-clock opioid analgesia and that it is critical to adjust the dosing regimen taking into account the patient's prior analgesic treatment experience; that opioid analgesics have a narrow therapeutic index in certain patient populations especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension; that the administration of Kadian may obscure the diagnosis or clinical course in patients with acute abdominal conditions; and that Kadian may aggravate pre-existing convulsions in patients with convulsive disorders. The Kadian PI also include several specific precautions related to cordotomy, use in pancreatic/biliary tract disease, tolerance and physical dependence, use in special risk groups (e.g., elderly or debilitated patients, patients with severe renal or hepatic insufficiency), and risks associated with driving or operating machinery.

The PI outlines several serious drug interactions with Kadian, including CNS depressants, muscle relaxants, mixed agonist/antagonist opioid analgesics, monoamine oxidase inhibitors, cimetidine, and diuretics.

In addition, the ADVERSE REACTIONS section of the PI states that the most serious adverse events occurring in patients taking Kadian include respiratory depression, respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock. The most frequent less severe adverse events include drowsiness, dizziness, constipation, and nausea.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. While the Comparison Detailer and the Co-Pay Assistance Program brochure include information from the boxed warning and some adverse reactions associated with Kadian, they fail to include other important and serious risk information. Specifically, the Comparison Detailer and Co-Pay Assistance Program brochure present several effectiveness claims for Kadian but fail to present any contraindications, and also omit several warnings, precautions, drug interactions and adverse events. For example the promotional materials fail to reveal warnings regarding potentially fatal abuse of opioids, use by individuals other than the patient for whom the drug was prescribed, interactions with alcohol and drugs of abuse, impaired respiration, head injury and increased intracranial pressure, hypotensive effect, interactions with other central nervous system depressants, gastrointestinal obstruction, and anaphylaxis. Similarly, the promotional materials fail to reveal precautions related to use in patients with prior analgesic treatment experience; use in certain patient populations with narrow therapeutic index for opioid analgesics; use in patients with acute abdominal conditions; use in patients with convulsive disorders; use in patients

undergoing cordotomy; use in pancreatic/biliary tract disease; tolerance and physical dependence with use of opioids; use in special risk groups; and risks associated with driving and operating machinery.

The Comparison Detailer also fails to present risk information with a prominence and readability that is reasonably comparable to the presentation of benefit information. Specifically, the first five of the six pages of the Comparison Detailer prominently present efficacy claims about Kadian using large, bolded headers and claims surrounded by a significant amount of white space, and using colorful charts and graphs. However, the only specific risk information presented is relegated to the back cover of the piece. Furthermore, this information is presented in small font in single-spaced paragraph format, and beneath a large, bolded headline claim that presents a benefit claim, "**Prescribe KADIAN® – Less pain for your patients. More options for you**" (emphasis in original). In addition, there are no presentation elements to emphasize to the reader that it is important safety information.

In addition, the Co-Pay Assistance Program brochure minimizes the serious and significant risks associated with the use of Kadian. Specifically, the back cover includes the boxed warning and some information from the ADVERSE REACTIONS section of the PI. However, these serious, potentially fatal risks are presented in highly complex, medically technical language that is not likely to be understood by consumers.

We note that the statement, "***Please see accompanying complete Prescribing Information***" (emphasis in original) appears on various pages of the Comparison Detailer and Co-Pay Assistance Program brochure; however this statement does not mitigate the misleading omission and/or minimization of risk information in the pieces.

The overall effect of these presentations minimizes the risks associated with Kadian and misleadingly suggests that Kadian is safer than has been demonstrated.

Broadening of Indication/Failure to State Full Indication

Promotional materials are misleading if they imply that a drug product is indicated for use in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. The Comparison Detailer and Co-Pay Assistance Program brochure fail to include the complete approved indication for Kadian, and present broad claims about the drug's use in treating pain, therefore implying that Kadian is appropriate for use in a broader range of patients than it is approved to treat. For example, the Comparison Detailer includes the following claims (emphasis in original):

- "**Allow for less breakthrough pain and more consistent pain relief for patients**" (footnote omitted)
- "**Better pain control**. . ."
- "**Improved pain control**. . ."
- "**Allow patients to live with less pain**. . ." (footnote omitted)
- "**Allow individualization and customization of a patient's pain treatment**"
- "**Prescribe KADIAN® – Less pain for your patients. More options for you**."
- "**Less Pain. More Options**."

These presentations in the Comparison Detailer suggest that Kadian is appropriate for patients with broader types of pain than the drug is indicated for. Similarly, the Co-Pay Assistance Program brochure includes the following statements (emphasis in original):

- "**Why is pain management important?** Pain management is a large part of your overall health care plan. Many Americans suffer from chronic or ongoing pain . . .Managing your pain the right way begins by talking to your healthcare provider. Discover the cause of your pain by taking note of what makes your pain start and what makes it worse."

- "**What is chronic pain?** Chronic pain is ongoing and can last longer than 6 months. Chronic pain can be mild or severe. . . ."

- "**How can I treat my chronic pain?** To help manage your pain, your healthcare provider will determine what level of pain control you need. Depending on what kind of pain you have and how it affects your life, your healthcare provider will choose a drug that works just for you."

The totality of these presentations in the Co-Pay Assistance Program brochure suggests that patients with broader types of chronic pain than the drug is indicated for are appropriate candidates for Kadian therapy, when this is not the case. These presentations in the two pieces are particularly concerning considering the serious and potentially fatal risks associated with the drug. Kadian is only appropriate for a very limited patient population who experience pain. We note that the partial indication of Kadian is included on the back covers of both pieces (included as warnings in the Comparison Detailer). However, these presentations omit the important limitation that:

> KADIAN® is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. KADIAN® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate.

In addition, the partial indication included on the back cover of the Co-Pay Assistance Program brochure, unlike the chronic pain information, is written in technical medical language that is not likely to be easily understood by consumers. We also note that the statement, "***Please see accompanying complete Prescribing Information***" (emphasis in original) appears on various pages of the Comparison Detailer and Co-Pay Assistance Program brochure; however this statement does not mitigate the implication of the above claims and presentations that broadly promote the use of this drug for any type of pain relief. Therefore, the pieces misleadingly suggest that Kadian can be used for pain relief in a much broader range of patients than has been demonstrated by substantial evidence or substantial clinical experience.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they represent or suggest that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. The Comparison Detailer includes the following efficacy claims and presentations that compare Kadian to MS Contin® (morphine sulfate controlled-release) Tablets, CII (MS Contin) and generic controlled-release morphine (emphasis in original):

- "**Why settle for generic MS Contin® tablets. . .When you can prescribe the benefits of KADIAN® capsules?**"

- "**Fewer peaks and valleys**
  Smooth steady-state plasma levels compared with controlled-release (CR) morphine tablets q12h and q24h"[2] presented in conjunction with the following two graphs:

  - Graph titled, "Pharmacokinetics of **ONCE-DAILY KADIAN®** vs twice-daily CR morphine tablets over 24 hours"[2,3] that displays normalized mean steady-state plasma morphine concentration (ng/mL) over time (hours) of Kadian and CR morphine tablets.

  - Graph titled, "Pharmacokinetics of **TWICE-DAILY KADIAN®** vs twice-daily CR morphine tablets over 12 hours"[2,3] that displays normalized mean steady-state plasma morphine concentration (ng/mL) over time (hours) of Kadian and CR morphine tablets.

- "**Allow for less breakthrough pain and more consistent pain relief for patients**"[3]

The above claims and presentations misleadingly imply that Kadian has been shown to be superior to MS Contin or generic controlled-release morphine because Kadian's pharmacokinetic properties will lead to less breakthrough pain and more consistent pain relief. FDA is not aware of any substantial evidence or substantial clinical experience that supports these claims and presentations. If you have data to support these claims, please submit the data to FDA for review.

The Comparison Detailer references Kadian's PI to support the above claims and presentations. The CLINICAL PHARMACOLOGY, Pharmacokinetics and Absorption sections of the PI include data from 48 patients with pain related to malignancy that were enrolled in two pharmacokinetic studies. The results from these two studies suggest less fluctuation in steady-state plasma concentrations (C_{max}-C_{min}/C_{min}) normalized to 100 mg every 24 hours in patients who were given Kadian compared with patients who were given twice daily controlled-release morphine tablets. However, the clinical consequences of these

[2] KADIAN® [current prescribing information].
[3] Gourlay GK, Cherry DA, Onley MM, et al. Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly MS Contin in the treatment of severe cancer pain. *Pain*. 1997;69(3):295-302.

pharmacokinetic differences were not studied and are not known. It is at least possible that the earlier and higher peak leads of MS Contin could represent an advantage absent clinical pain data. The pharmacokinetic data presented within the PI do not constitute substantial evidence to support any claims of clinical superiority such as those described above.

The Comparison Detailer also references the Gourlay, et al. article, which describes one of the pharmacokinetic studies presented in the PI (Study# MOR-9/92), to support the above claims and presentations. The study results in the Gourlay, et al. article reported that patients who were given Kadian had significantly higher C_{min} concentrations, less fluctuation in plasma morphine concentrations throughout the dosing interval, and a greater time that plasma concentrations were ≥75% of C_{max} compared to patients who were given MS Contin. Unlike the PI, Gourlay, et al. also reports pain results from this study. Gourlay, et al. found no significant differences between Kadian and MS Contin in any of the steady-state (day seven) primary clinical parameters (i.e., percent taking rescue medication, time to first rescue dose, total strength of rescue dose, and percent total 24-hour morphine dose as rescue dose). In addition, there were no differences in steady-state secondary parameters, including verbal rating scale for pain intensity and control or visual analog pain scores. The Gourlay, et al. article thus provides no support for the idea that the pharmacokinetic differences between Kadian and MS Contin had any clinical consequences.

In addition, the Comparison Detailer includes the following pain and sleep-related claims and presentations that compare Kadian to MS Contin and generic controlled-release morphine (emphasis in original):

- "**Better pain control and improved sleep scores**"
- "**Improved pain control and sleep scores in patients treated with KADIAN® who were previously on CR morphine tablets**"[4*] presented in conjunction with the following two graphs:
  - Graph titled, "Significant **PAIN REDUCTION**"[4] that displays a "**36% improvement in pain score**"[4] (scale 0-10: 0=no pain; 10=worst pain imaginable) from baseline in patients switched from MS Contin to Kadian.
  - Graph titled, "Significant **REDUCTION IN SLEEP INTERFERENCE**"[4] that displays a "**47% improvement in sleep score**"[4] (scale 0-10: 0=did not interfere with sleep at all; 10=completely interfered with sleep) from baseline in patients switched from MS Contin to Kadian.
- "**Allow patients to live with less pain and get adequate rest with less medication**"[4]

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[4] Weil A, Nicholson B, Ross E, Sasaki J. Patients with chronic, non-malignant, moderate/severe pain can be successfully switched from other sustained-release morphine or oxycodone compounds of Kadian® (morphine sulfate sustained-release capsules): the KRONUS-MSP trial. Poster presented at: American Pain Society 23rd Annual Scientific Meeting; May 6-9, 2004; Vancouver, BC.

* In a subanalysis of a randomized, open-label, blinded endpoint study of patients previously taking CR morphine tablets and switched to KADIAN® capsules.

These claims are supported by a historically controlled study of inadequate design, completely lacking any concurrent control. The above claims and presentations misleadingly imply that Kadian is superior to MS Contin and generic controlled-release morphine because Kadian provides better pain control and a reduction in sleep interference compared to MS Contin and generic controlled-release morphine. FDA is not aware of any substantial evidence or substantial clinical experience to support such a claim.

The Comparison Detailer references the Weil, et al. poster presentation[4] to support the above claims and presentations. This reference discusses the KRONUS-MSP trial—a study that was not published. Data for the KRONUS-MSP trial was derived from a community-based, prospective, open-label, blinded endpoint trial that included a subset of patients who were previously and unsuccessfully treated with either MS Contin (n=55) or OxyContin® (oxycodone HCl controlled-release) Tablets, CII (OxyContin) (n=150). The patients were randomized to receive either morning or evening daily dosing with Kadian during a four-week treatment period. No patients were randomized to MS Contin or OxyContin. For several reasons, the cited reference fails to support any claim of superiority of Kadian to MS Contin. We note that referring to this trial as "randomized" is itself misleading, as a reader would surely assume that randomization was to two drug treatments, not to morning and evening dosing, a distinction not remotely relevant to the data presented.

The study compared pain reduction and interference of pain with sleep in people reported to have had a poor response to prior treatment with MS Contin or OxyContin. An appropriate study design to investigate this question would have randomized patients to Kadian or MS Contin. A finding in such a properly designed study of greater effect on pain or sleep would not support a general claim of superiority but could support the value of Kadian in MS Contin poor responders. The trial as conducted, however, compared results on open-label treatment with Kadian with an historical control MS Contin cohort. This is a completely meaningless comparison. It is commonly observed that patients given a placebo in trials improve compared to their pre-trial state. That is why, in symptomatic continuous pain, a concurrent control group is essential.

Overall, data from the KRONUS-MSP trial clearly do not support any conclusion that Kadian is superior to alternative treatments in pain or sleep measures. The trial was an exploratory open-label study with no comparators; thus, no conclusions can be inferred. If you have data from adequate and well-controlled trials to support these claims, please submit them to FDA for review.

Finally, the Comparison Detailer includes the following dosing claims and presentations that compare Kadian with both MS Contin and AVINZA® (morphine sulfate extended-release capsules), CII (Avinza) (emphasis in original):

- "**Fewer barriers to prescribing**
  The unique dosing flexibility of KADIAN® gives you more options with a morphine"[2,5,6] presented in conjunction with a chart comparing the available capsule and tablet dose strengths for Kadian, MS Contin, and Avinza.

- Claims below the chart include the following:

  - "No immediate-release (IR) component"
  - "No ceiling dose—contains no acetaminophen, ibuprofen, or fumaric acid"[2]
  - "Allows for titration in increments of 10 mg, with a low dose of 10 mg"[2]
  - "**Allow individualization and customization of a patient's pain treatment**"

These claims are misleading because they imply that Kadian is superior to both MS Contin and Avinza because Kadian's dosage strength availability (i.e., eight dosage strengths in 10, 20, 30, 50, 60, 80, 100, and 200 mg capsules) offers "fewer barriers to prescribing," and because Kadian has no immediate release component, no ceiling dose, and allows for 10 mg titration increments. The Comparison Detailer references the PIs for Kadian, Avinza, and MS Contin to support these claims. However, FDA is unaware of any substantial evidence or substantial clinical experience to support the claim that the above dosing characteristics allow Kadian to have "fewer barriers to prescribing" (the meaning of which is not clear) as compared to other extended-release morphine products. There is no evidence to support that small increments in dosage strength (i.e., 10 mg) would offer a clinical advantage for Kadian in patients who are taking an opioid chronically, particularly as Kadian may need to be dosed more often than some of the comparators (e.g., twice a day versus once a day for Avinza). There is no evidence to support that an immediate-release component would limit the use of a morphine product. Finally, the claim suggesting that Kadian offers fewer barriers to prescribing because it does not contain acetaminophen, ibuprofen, or fumaric acid is misleading because this characteristic of Kadian does not offer any advantages over other extended-release morphine products. Specifically, none of the extended-release morphine products contain acetaminophen or ibuprofen, and while Avinza contains fumaric acid, there is no evidence to suggest that the resulting limiting dose would pose any restrictions on the typical patient population for which the drug is indicated.

Unsubstantiated Effectiveness Claims

Promotional materials are misleading if they contain representations that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The Co-Pay Assistance Program brochure includes the following presentations:

- ". . . Many Americans suffer from chronic or ongoing pain. It can cause you to miss work and can even keep you from enjoying life. If left untreated, pain can place stress on your body and your mental health. . . ."

- ". . . Chronic pain . . . can be inconvenient and can keep you from your daily tasks."

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[5] AVINZA® [prescribing information]. Bristol, TN: King Pharmaceuticals Inc; October 2005.
[6] MS Contin® [prescribing information]. Stamford, CT: Purdue Pharma LP; August 2007.

FDA acknowledges that the treatment of patients in pain is a critical aspect of medical practice. Although Kadian may help treat patients' moderate to severe pain, we are not aware of substantial evidence or substantial clinical experience demonstrating that the magnitude of the effect the drug has in alleviating pain, taken together with any drug-related side effects patients may experience (such as the common adverse events of drowsiness, dizziness, constipation and nausea), results in an overall positive impact on a patient's work, physical and mental functioning, daily activities, or enjoyment of life. In addition, we are not aware of any studies demonstrating that the level of pain reduction experienced by patients on Kadian therapy corresponds with a positive impact on the outcomes claimed. If you have data to support these claims, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the Comparison Detailer and Co-Pay Assistance Program brochure misbrand Kadian in violation of the Act, 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (ii) & (xviii); (e)(7)(i) & (viii).

DDMAC requests that Actavis immediately cease the dissemination of violative promotional materials for Kadian such as those described above. Please submit a written response to this letter on or before March 4, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Kadian that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials.

Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to MACMIS#18148 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Kadian comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20616	ORIG-1	ACTAVIS ELIZABETH LLC	KADIAN (MORPHINE SULFATE) ER CAPS 20/50

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS W ABRAMS
02/18/2010


actavis
think smart medicine

Faulding Inc.
A Division of F.H. Faulding & Co. Limited Incorporated in South Australia

28 June 1995

Dr. Robert Bedford, Acting Director
Pilot Drug Evaluation Division
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Room 9B-23, HFD-007
Rockville, Maryland, 20857

Re: New Drug Application 20-616
KADIAN™ Morphine Sulfate Sustained-release Capsules, 20 mg, 50 mg and 100 mg

Dear Dr. Bedford:

In accordance with the regulations promulgated under Section 505 of the Federal Food Drug and Cosmetic Act as amended, Faulding Inc., a division of F.H. Faulding & Company Limited, is submitting this New Drug Application for KADIAN™ Morphine Sulfate Sustained-release Capsules, 20 mg, 50 mg and 100 mg.

KADIAN™ is indicated for the management of pain where treatment with an opioid analgesic is indicated for more than a few days.

KADIAN™ was developed for use in patients with chronic pain who require repeated dosing with potent opioid analgesics, and has been tested in patients with pain due to a variety of malignant conditions.

The rationale on which KADIAN™ is based, is the development of a truly sustained-release product which minimizes the peak to trough ratio of the concentration of morphine in plasma by controlling the rate of drug release from polymer-coated pellets. This provides a dosage form which may be taken every 12 or 24 hours improving patient convenience and compliance and may reduce the incidence of opioid-related adverse effects and the incidence of breakthrough pain, and thus improve the quality of care for relief of pain.

The clinical development program for KADIAN™ was developed in association with the Pilot Drug Evaluation Staff of the Food and Drug Administration through the Interactive IND Process. The program consisted of eleven pharmacokinetic studies and six clinical efficacy and safety studies.

Studies have been conducted to characterize various aspects of the bioavailability and performance of the KADIAN™ delivery system under single-dose and steady-state conditions in both healthy subjects and patients with cancer pain. The safety and efficacy of KADIAN™ has been established in patients with cancer pain with profiles similar to that of immediate release morphine sulfate solution and controlled-release morphine sulfate tablets.

200 Elmora Avenue, Elizabeth NJ 07207 USA
TEL: +1-908-527-9100 • +1-800-526-6978
FAX: +1-908-558-1589

The data provided indicate that:

- After a single dose and at steady state, KADIAN™ has a true sustained-release pharmacokinetic profile when compared to immediate release morphine sulfate solution and controlled-release morphine sulfate tablets;
- In the management of moderate to severe chronic pain, KADIAN™ administered both every 24 hours and every 12 hours has an efficacy and safety profile clinically and statistically similar to that of immediate release morphine sulfate solution and controlled-release morphine sulfate tablets;
- Patients stabilized to adequate clinical effect with other morphine formulations may be safely and effectively transferred to KADIAN™ at the same total daily morphine dose; and,
- During the long-term open-label studies of KADIAN™, there was no indication of diminution of analgesia in patients with cancer pain treated for up to 24 months.

Effective drug therapy is the cornerstone of cancer pain management. Opioid analgesics are effective, easily titrated to analgesic effect and as a class have a favorable benefit-to-risk ratio. KADIAN™ has demonstrated in clinical efficacy studies that it is an effective strong analgesic drug product. The risks associated with treatment with KADIAN™ are similar to those for other morphine products.

The contents of this submission are organized in the following manner:

Volume 1	**Item 13**	Patent Information
	Item 15	Other Information
	Item 1	Index
	Item 2	Application Summary
Volumes 2-18	**Item 3**	Chemistry, Manufacturing and Controls
Volumes 19-20	**Item 4a**	Samples
	Item 4b	Methods Validation Package
Volume 21	**Item 4c**	Labeling
Volumes 22-25	**Item 5**	Non-clinical, Pharmacology & Toxicology
Volumes 26-58	**Item 6**	Human Pharmacokinetics and Bioavailability
Volumes 59-103	**Item 8**	Clinical
Volumes 104-136	**Item 10**	Statistics
Volumes 137-148	**Item 11**	Tabulations
Volumes 149-189	**Item 12**	Case Report Forms

If you have any questions, please contact me directly in New Jersey at (908) 527-9100.

Yours sincerely,

Faulding Inc.

George Wagner
Manager, Regulatory Affairs

Enclosures

CC: Heike Carmichael, F.H. Faulding & Co. Ltd.
Frank Sasinowski, Hymen, Phelps and McNamara

Faulding Inc.
A Division of F.H. Faulding & Co. Limited Incorporated in South Australia

UPS OVERNIGHT COURIER

July 05, 1995

Heather L. Pedersen
Newark District Pre-Approval Program Manager
North Brunswick Resident Post
120 North Center Drive
North Brunswick, New Jersey 08902

Dear Ms. Pedersen:

In accordance with 21 CFR 314.50, Faulding Inc. hereby submits a Field Copy of our New Drug Application for KADIAN™ Morphine Sulfate Sustained-release Capsules, 20 mg, 50 mg and 100 mg. The Field Copy contains the Chemistry, Manufacturing and Controls Section of the application, the application form (Form FDA 356(h)), and a certification that the Field Copy is a true copy of the Chemistry, Manufacturing and Controls Section contained in the Archival and Review Copies of the application.

In accordance with 21 CFR 314.60 and 314.71, Faulding will submit Field Copies of all amendments and supplements to this application as they are generated and submitted to the Agency.

If you have any questions concerning this submission, please do not hesitate to contact me at (908) 527-9100 EXT. 337.

Sincerely,

Faulding Inc.

George Wagner
Manager, Regulatory Affairs

Enclosure

cc: H. Carmichael, Manager, Regulatory Affairs - Faulding Pharmaceuticals
D. Karaban, Director of Compliance - Purepac Pharmaceuticals

200 Elmora Avenue, Elizabeth NJ 07207 USA
TEL: +1-908-527-9100 • +1-800-526-6978
FAX: +1-908-558-1589

Index

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: April 30, 1994.
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT Faulding Inc. (a division of F.H. Faulding & Co. Limited)	DATE OF SUBMISSION 29 June 1995
ADDRESS *(Number, Street, City, State and Zip Code)* 200 Elmora Avenue Elizabeth, NJ 07207	TELEPHONE NO. *(Include Area Code)* (908) 527-9100
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) 20-616

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
KADIAN (Morphine Sulfate Sustained-Release Capsules)	KADIAN

CODE NAME *(If any)*	CHEMICAL NAME
MOLLY KAPANOL	MORPHINE SULFATE

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
CAPSULE	ORAL	20mg 50mg 100mg

PROPOSED INDICATIONS FOR USE

KADIAN is indicated for the management of pain where treatment with an opioid analgesic is indicated for more than a few days.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

IND #35,553 - Kapanol (encapsulated polymer-coated sustained release morphine sulfate pellets) - Faulding Pharmaceuticals

DMF Type 1 #5685 - Faulding Pharmaceuticals (A division of F.H. Faulding & Co. Limited)

SEE ATTACHED LIST OF DMF REFERENCES

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Summary (21 CFR 314.50 (c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
X	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
X	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (21 CFR 314.50 (d) (6))
X	11. Case report tabulations (21 CFR 314.50 (f) (1))
X	12. Case reports forms (21 CFR 314.50 (f) (1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
X	15. OTHER *(Specify)* Bioavailability Waiver for 100 mg and 20 mg KADIAN™ Capsules, Exclusivity information and Pentium Chip Certification.

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
George Wagner Regulatory Affairs Manager		28 JUNE 1995

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
200 Elmora Avenue Elizabeth, NJ 07207	(908) 527-9100

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

NDA 20-616

ATTACHMENT to FORM FDA 356h

FAULDING INC.
KADIAN™ MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES

List of drug master files referred to in this application:

DMF Holder	DMF No.
Quantum Chemical Co.	885
Noramco of Delaware Inc.	5775 6967
Mallinckrodt Chemical Inc.	5857
Capsugel	3367
Tek Products & Services, Inc.	6995
Ampacet	8354 8763
Drug Plastics & Glass Company, Inc.	1933
American White Cross (Formerly: National Patent Medical)	4164
Carolina Absorbent (Cotton Co)	6855
Solvay Polymers, Inc.	3720
Lyondell Polymers	5036
Van Blarcom Closures, Inc.	5828
Mold-Rite Plastics, Inc.	9775
3 M Corporation	3782
Paco Pharmaceutical Services, Inc.	3347
Klockner Pentaplast of America, Inc.	3764
Reynolds Metals Company	984
Chevron Chemical Company	1572
Eastman Chemcial Company	9522

000003

ITEM 13 PATENT INFORMATION

The following patent information is submitted by Faulding, in accordance with 21 CFR Part 314.53(c), is relevant to the product the subject of this New Drug Application, Kadian™ Morphine Sulfate Sustained-release Capsules, 20mg, 50mg and 100mg.

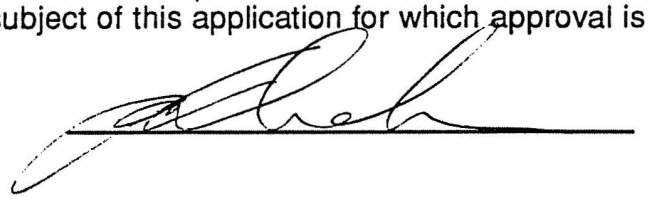
A. PATENT INFORMATION

1.	**Patent Number:**	**5,202,128**
	Expires:	13 April, 2010
	Type:	Drug Product Patent
	Owner:	F. H. Faulding & Co. Limited, Australia
	Agent:	Mr George Wagner Regulatory Affairs Manager Faulding Inc. 200 Elmora Avenue Elizabeth NJ 07207
2.	**Patent Number:**	**5,378,474**
	Expires:	23 March, 2010
	Type:	Drug Product Patent
	Owner:	F. H. Faulding & Co. Limited, Australia
	Agent:	Mr George Wagner Regulatory Affairs Manager Faulding Inc. 200 Elmora Avenue Elizabeth NJ 07207

000004

B. DECLARATIONS

1. The undersigned declares that Patent No. 5,202,128 covers the formulation or composition of Kadian™ Morphine Sulfate Sustained-release Capsules. This product is the subject of this application for which approval is being sought.

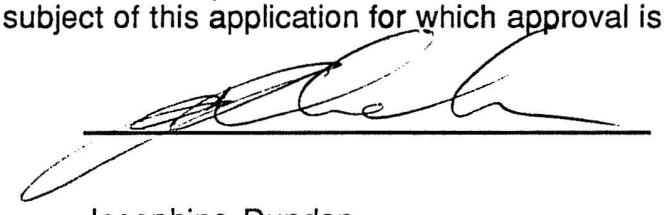
Signature: 

Name: Josephine Dundon

Title: Group Manager, Intellectual Property & Legal Services

Date: 28 June 1995

2. The undersigned declares that Patent No. 5,378,474 covers the formulation or composition of Kadian™ Morphine Sulfate Sustained-release Capsules. This product is the subject of this application for which approval is being sought.

Signature: 

Name: Josephine Dundon

Title: Group Manager, Intellectual Property & Legal Services

Date: 28 June 1995

000005

EXCLUSIVITY INFORMATION

The following information is submitted by Faulding, in accordance with 21 CFR Parts 314.50(j) and 314.108(b)(4), in support of a claim for exclusivity for the product the subject of this New Drug Application, Kadian™ Morphine Sulfate Sustained-release Capsules, 20mg, 50mg and 100mg.

1. Faulding claims exclusivity under 21 CFR Part 314.108(b)(4) for Kadian™ Morphine Sulfate Sustained-release Capsules 20mg, 50mg and 100mg, the product the subject of this application for which approval is being sought.

2. Faulding claims exclusivity under 21 CFR Part 314.108(b)(4) on the basis that, this application:

   (i) has been submitted under section 505(b) of the Act;

   (ii) will be approved after September 24, 1984;

   (iii) is for a drug product that contains an active moiety, morphine sulfate, that has been previously approved in another application under section 505(b) of the Act; and

   (iv) contains reports of clinical investigations conducted or sponsored by Faulding that are essential to approval of the application as made.

3. Faulding certifies that, to the best of its knowledge, the clinical investigations included in this application meet the definition of "new clinical investigations" as set forth in 21 CFR Part 314.108(a).

   Faulding further certifies that it has thoroughly searched the scientific literature and to the best of its knowledge and belief, there are no published studies which adequately support the indications and labeling proposed by Faulding for the product the subject of this NDA, Kadian™ Morphine Sulfate Sustained-release Capsules 20mg, 50mg and 100mg. Further, no morphine sulfate product approved for marketing in the US, has been approved for administration under a once-a-day or twice-a-day dosing schedule.

   Faulding further certifies that all clinical studies included in this application have been conducted by F. H. Faulding & Co. Limited as named in the forms FDA-1571 for the investigational new drug application (IND#35,553) under which the new clinical investigations were conducted. Faulding Inc, the sponsor of this application, is a wholly owned US subsidiary of Faulding.

000006

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Mr George Wagner
Regulatory Affairs
Faulding Pharmaceuticals
Elmora Avenue
Elizabeth, New Jersey 07207

December 2, 1994

Dear George

Re: Waiver of bioavailability study for 100mg and 20mg Kapanol[R] capsules.

This is to advise that the Agency has considered your request for the waiver of a bioavailability study comparing 100mg Kapanol[R] capsules manufactured at different sites.

In the interests of the safety of the individuals participating in the bioavailability study and given that Faulding Ltd. intend to conduct a bioequivalence study comparing 50 mg doses manufactured at the Australian and U.S.A. sites, a waiver is granted provided that;

1. evidence is submitted which demonstrates that each dosage strength manufactured at either site is proportionally similar with regard to the active and inactive ingredients;

2. the 50mg, 20mg and 100mg product meet an appropriate in vitro test approved by the F.D.A.

The waiver of a bioequivalence study comparing 100mg dosage strengths is also applicable to the 20mg dosage strength.

Yours sincerely;

P A Lockwood.

Peter Lockwood (Pharmacokinetic Reviewer).

HFD007/MCNEALE, LOCKWOOD
~~HFD19/FOI~~
HFD007/IND 35553 original + division file

000007

HARRIS
624 Peach Street
P.O. Box 80837
Lincoln, NE 68501
(402) 476-2811
Fax: (402) 476-7598

January 26, 1995

To Whom It May Concern:

This letter is to certify that Harris Laboratories, Inc., has not used any computer utilizing a Pentium chip in the analysis or handling of data for any project.

Sincerely,

James E. McClurg, Ph.D.
President and CEO
Life Sciences

000008

NORAMCO OF DELAWARE INC.

500 OLD SWEDES LANDING ROAD • WILMINGTON, DELAWARE 19801-4417
302-652-3840 • FAX 302-652-4417

August 11, 1994

Food and Drug Administration
Center for Drug Evaluation & Research
Central Document Room
12420 Parklawn Drive
Room 2 - 14
Rockville, MD 20852

RE: Drug Master File No. 5775 and 6967

Gentlemen:

We hereby authorize FDA to refer to Type I Drug Master File (DMF) No. 5775 and to Type II DMF No. 6967, in support of any IND or NDA, including amendments or supplements thereto, filed by Faulding, A Division of F.H. Faulding & Co., Ltd., 1538 Main North Road, Salisbury S. Australia, 5108 Australia, for any product which utilizes our Morphine Sulfate, USP, in the manufacture or packaging of their product.

By copy of this letter, we also authorize Faulding, A Division of F.H. Faulding & Co., Inc. to incorporate by reference Type I DMF No. 5775 and Type II DMF No. 6967, in any IND or NDA utilizing our Morphine Sulfate, USP, including any amendments or supplements thereto, submitted to FDA.

The information contained in Type I DMF 5775 and Type II DMF 6967 should be held confidential in conformance with 21 CFR Part 20 and 21 CFR 314.430.

We certify that all operations, procedures and materials used will be in conformance with said Master Files, with notification of any change made to Faulding, A Division of F.H. Faulding & Co., Ltd. Furthermore, we certify that the methods, facilities and controls employed are in conformance with Current Good Manufacturing Practice as applicable to bulk pharmaceutical chemicals.

Sincerely,

Edward F. Kowalski
Quality Assurance Administrator

000009

To: Andy Fox

MALLINCKRODT CHEMICAL

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777

Telephone (314) 530-2000
Facsimile (314) 530-2505

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

January 10, 1995

Drug Master File Staff
Food and Drug Administration
12420 Parklawn Drive, Room 2-14
Rockville, Maryland 20852

Subject: DMF #5857 - Morphine Sulfate

You are hereby authorized to reference Mallinckrodt's Type II DMF #5857 for Morphine Sulfate, Code 1516, in support of INDAs, NDAs, NADAs, and ANDAs submitted by:

Faulding, A Division of F.H. Faulding & Co. Ltd.
1538 Main North Road
Salisbury, South Australia
5108 Australia

Thank you.

Sincerely,

Charles H. Smith

Charles H. Smith
Responsible Agent

cc: G. Rozman
B. Spencer

000010

JAN 13 '95 01:53PM M.C. BULK NARCOTICS P.1/1

Pharmaceutical
Research

PARKE-DAVIS

Sean Brennan, Ph.D.

February 1, 1995

Re: Type IV Drug Master File No. 3367
Letter of Authorization

Drug Master File Staff
Food and Drug Administration
12420 Parklawn Drive, Room 2-14
Rockville, Maryland 20852

Dear Sir/Madam:

We, Parke-Davis, as the agent for Capsugel, Division of Warner-Lambert Company with main offices located at 201 Tabor Road, Morris Plains, New Jersey, 07950, do hereby authorize the Food and Drug Administration to refer to our Type IV Capsule DMF 3367, Greenwood, South Carolina facility on behalf of:

Faulding
A Division of F.H. Faulding Co. LTD
1538 Main North Road
Salisbury, South Australia 5108
AUSTRALIA

in support of any IND, NDA or ANDA submission for the above company's encapsulated drug products utilizing our gelatin capsules manufactured at the Greenwood facility.

The empty gelatin capsules supplied to the above company will be produced in conformance with the methods and procedures as outlined in the Drug Master File No. 3367 which was last updated February 4, 1994. The pages that pertain to empty gelatin capsule specifications are:

Page 33-34 - Components list

Page 35 - Reference to the Capsules Specification sheet supplied to our customers for inclusion in their submission

Page 38-51 - Manufacturing Information, Techniques and Materials of a Proprietary Nature.

We certify that to the best of our knowledge the methods used in, and the facilities and controls used for the manufacture, processing, packing, and holding of the empty gelatin capsules conform to Current Good Manufacturing Practices as set forth in 21 CFR Parts 110, 210 and 211. We further certify that all dyes are from FDA certified batches, and all other materials used in the manufacture of the empty gelatin capsules meet the Food Additives Regulations.

It is understood that the information contained in DMF No. 3367 shall be treated as confidential in accordance with the provisions of the Federal Food, Drug and Cosmetic Act and Code of Federal Regulations.

Should you have any questions regarding this submission, please contact me at 313/996-7596 or FAX 313/996-7890.

Sincerely,

Alexander J. Brankin Jr.
for Sean Brennan

SB/rp
m:/dmf/3367/13095.fda

000012

TEK Products & Services, Inc.
530 Crestmont Street, Reading, PA 19611
Phone (610) 376-0690 FAX (610) 376-6510

February 22, 1995

Food and Drug Administration
Center for Drugs and Biologics
Central Document Room
12420 Parklawn Drive, Room 2-14
Rockville, MD 20852

Dear Sir/Madam:

Identification of DMF

DMF Number Assigned:	DMF 6995
Date of Submission:	February 22, 1995
Title of Submission:	Type IV; Imprinting Inks for Marking Pharmaceutical Dosage Forms
Holder of Submission:	Tek Products & Services, Inc.
Submitted By:	Tek Products & Services, Inc.
Agent(s):	None

By copy of this correspondence, I am granting Faulding, A Division of F.H. Faulding Ltd., 1538 Main North Road, Salisbury, South Australia, 5108 Australia, access to information regarding the following Imprinting Ink Formulae from the DMF specified above:

	DMF 6995 Page No.
TekPrint™ SW-9009 Black	I-909

Please add this access letter at page number F2 - 1. Thank you for your time and consideration.

Sincerely,

Donald N. Lykens

Donald N. Lykens
President

DNL:pml

cc: Mr. Andy Fox

Quantum Chemical Company

Quantum

Allen Research Center
11530 Northlake Drive
P.O. Box 429566
Cincinnati, OH 45249
513-530-6500

DRUG MASTER FILE #885

May 17, 1995

Drug Master File Staff
Food and Drug Administration
12420 Parklawn Drive, Room 2-14
Rockville, MD 20852

Gentlemen:

This is to grant permission to the FDA to consult Quantum Chemical Company, DMF 885 to determine the suitability of PETROTHENE® LR 7340-43 (formerly LR 734-43) used in a pharmaceutical product application by F.H. Faulding, 200 Elmora Avenue, Elizabeth, NJ 07207, attention: Ms. Liz Reilly.

LR 7340-43 is molded by Drug Plastics & Glass, One Bottle Drive, Boyertown, PA 19512, attention: Mr. Ross Campbell.

This is also to inform the FDA that the LR 7340-43 filing we made 4/16/93 still describes our LR 7340-43.

Sincerely,

Bernard Henn/ss

Bernard Henn
Coordinator of Regulatory Affairs
Product Applications Safety

BH:ss

copy: Ms. Liz Reilly
Pure Pac Pharmaceuticals Co.
200 Elmora Avenue
Elizabeth, NJ 07207

000014

Quantum Chemical Company

Quantum

Allen Research Center
11530 Northlake Drive
P.O. Box 429566
Cincinnati, OH 45249
513-530-6500

DRUG MASTER FILE #885

May 17, 1995

Drug Master File Staff
Food and Drug Administration
12420 Parklawn Drive, Room 2-14
Rockville, MD 20852

Gentlemen:

This is to grant permission to the FDA to consult Quantum Chemical Company, DMF #885 to determine the suitability of PETROTHENE® LR 7320-00 high-density polyethylene used in a pharmaceutical product application by F.H. Faulding, 200 Elmora Avenue, Elizabeth, NJ 07207, attention: Ms. Liz Reilly.

LR 7320-00 is molded by Drug Plastics & Glass, One Bottle Drive, Boyertown, PA 19512, attention: Mr. Ross Campbell.

This is also to inform the FDA that the LR 7320-00 filing we made 4/16/93 still describes our LR 7320-00.

Sincerely,

Bernard Henn/ss

Bernard Henn
Coordinator of Regulatory Affairs
Product Applications Safety

BH:ss

copy: Ms. Liz Reilly
Pure Pac Pharmaceuticals Co.
200 Elmora Avenue
Elizabeth, NJ 07207

Ampacet

May 18, 1995

FOOD & DRUG ADMINISTRATION
Central Document Room
Center for Drug Evaluation and Research
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20852

RE: Drug Master File No. DMF8354;
11078 White PE MB

Dear Sirs:

We are advised that **F.H. Faulding** (200 Elmora Ave, Elizabeth, NJ 07207) has submitted, or will be submitting, a New Drug Application or Abbreviated New Drug Application. In this regard, they are proposing the use of our product designated as **11078 White PE MB.**

We have data on file concerning this product in a Type III Confidential Food and Drug Administration Drug Master File (DMF) No. 8354.

We hereby authorize the Food and Drug Administration to make reference to the data we have supplied in this DMF in connection with any F.H. Faulding New Drug Application or supplements thereto for 11078. Of course, it is requested that the data be maintained as confidential to the Food and Drug Administration as set forth in Section 314.430 dealing with the confidentiality of data in New Drug Applications and Abbreviated New Drug Applications and FDA's Public Information Regulations set forth in 21 C.F.R. Part 20.

We thank you for your attention to this matter.

Sincerely,

Denise R. Holl
Manager, Safety & Environmental

DRH/gf

cc: Ms. Liz Reilly - F.H. Faulding
Mr. Ross Campbell - Drug Plastics & Glass
Mr. Joe Schembri - Ampacet

000016

Ampacet Corporation • 660 White Plains Road • Tarrytown, N.Y. 10591-5130
Tel. (914) 631-6600 Admin. Fax (914) 631-7197
Mfg. Fax (914) 631-0556 Sales Fax (914) 631-7278

Ampacet

May 18, 1995

FOOD and DRUG ADMINISTRATION
Central Document Room
Center for Drug Evaluation and Research
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20852

Re: Drug Master File No. DMF 8763;
11447 White PE MB

Dear Sirs:

We are advised that **F.H. Faulding** (200 Elmora Ave, Elizabeth, NJ 07207) has submitted, or will be submitting, a New Drug Application or Abbreviated New Drug Application. In this regard, they are proposing the use of our product designated as **11447 White PE MB.**

We have data on file concerning this product in a Type III Confidential Food and Drug Administration Drug Master File (DMF) No. 8763.

We hereby authorize the Food and Drug Administration to make reference to the data we have supplied in this DMF in connection with any F.H. Faulding New Drug Application or supplements thereto for 11447. Of course, it is requested that the data be maintained as confidential to the Food and Drug Administration as set forth in Section 314.430 dealing with the confidentiality of data in New Drug Applications and Abbreviated New Drug Applications and FDA's Public Information Regulations set forth in 21 C.F.R. Part 20.

We thank you for your attention to this matter.

Sincerely,

Denise R. Holl

Denise R. Holl
Manager, Safety & Environmental

DRH/gf

cc: Ms. Liz Reilly - F.H. Faulding
Mr. Ross Campbell - Drug Plastics & Glass
Mr. Joe Schembri - Ampacet
DMF

000017

Ampacet Corporation • 660 White Plains Road • Tarrytown, N.Y. 10591-513
Tel. (914) 631-6600 Admin. Fax (914) 631-719
Mfg. Fax (914) 631-0556 Sales Fax (914) 631-727

DRUG PLASTICS & GLASS COMPANY, INC.

A Family of Perfect Quality Bottlemakers
ONE BOTTLE DRIVE, BOYERTOWN, PA 19512
(610) 367-5000 FAX (610) 367-9800

April 19, 1995

Mr. Mark Matarese
Product Coordination Staff
New Drug Evaluation
Food and Drug Administration
Central Document Room
1240 Park Building, Rm. 2-14
Rockville, MD 20852

REFERENCE; DMF-1933

Dear Mr. Matarese:

We hereby authorize you to incorporate, by reference, said Master File in consideration of products filed by Faulding, Inc., Division of F. H. Faulding & Co., Ltd., 1538 Main North Road, Salisbury, South Australia, 5108 Australia, Attn: Ms. Liz Reilly.

Reference is made to our Master File DMF-1933 for packaging components. DMF-1933 contains one volume and was most recently updated January 31, 1995.

We wish to advise you and we have represented to Ms. Liz Reilly, Faulding, Inc., Division of F. H. Faulding & Co., Ltd., 1538 Main North Road, Salisbury, South Australia, 5108 Australia, that the operations which we will perform in all respects conform to the description set forth in the said Drug Master File, and further that no changes will be made without prior approval by the Food and Drug Administration.

In your use of DMF-1933, please hold the information therein confidential to the extent possible under 21 CFR Par 20 and 21 CFR 314.430.

Very truly yours,

DRUG PLASTICS AND GLASS CO., INC.

Ross E. Campbell
Director of Quality

REC/mar

Encl.
cc: K. Scully,
L. Reilly (F. H. Faulding)

000018

AMERICAN WHITE CROSS

349 Lake Road
Dayville, CT 06241 USA
Tel: 203-774-8541
Fax: 203-774-1507

May 8, 1995

Drug Master File Staff
FOOD AND DRUG ADMINISTRATION
12420 Parklawn Drive
Room 2-14
Rockville, MD 20852

RE: DMF 4164 Cotton, Rayon and Polyester Coil

Dear Madam/Sir:

You are authorized to review AMERICAN WHITE CROSS Master File DMF 4164, and amendments thereto for Cotton, Rayon and Polyester Coil, in support of applications submitted by:

Faulding, Inc.
Division of F.H. Faulding & Co. Ltd.
1538 Main North Road
Salisbury, S. Australia 5108
Australia

The components, 6 gram Snopure Cotton Coil (Cat. #21166) and 12 gram Snopure Cotton Coil (Cat. #21246), included in the Master File, will be supplied to Faulding Inc. by AMERICAN WHITE CROSS, located at 349 Lake Road, Dayville, Connecticut, 06241.

We certify that these components will be manufactured as described in the Master File and will meet the specifications therein. Pertinent information for Snopure Coil may be found on pages 63, 64, 67, 89, 90, 91, 93, 94, 95, 96, 97, 99, 100, 102, 107, 108, 109, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 146, and 147.

No changes will be made without notifying Faulding Inc. and, if appropriate, amending our Drug Master File.

This permission and authorization shall not be construed to authorize divulging any information to Faulding Inc. or anyone else outside the Food and Drug Administration. We request that all information in the file be kept confidential within the meaning of 21 CFR, Section 314.420.

Sincerely,

Paul B. Callahan
Director, Quality Programs
AMERICAN WHITE CROSS

Carolina ABSORBENT COTTON CO.
MANUFACTURED WHERE GROWN
POST OFFICE BOX 34276
CHARLOTTE, NORTH CAROLINA 28234

April 26, 1995

Mr. Thomas J. McGinnis, R.Ph.
Food & Drug Administration
Central Document Room
12420 Parklawn Drive, Room 2-14
Rockville, Maryland 20852

MAY 1 1 1995

Dear Mr. McGinnis:

Please be advised that the Food & Drug Administration has the authorization to reference and review our Drug Master File, number 6855, for all of our Type III Pharmaceutical Coil products as manufactured in our plant in Charlotte, North Carolina, on behalf of Faulding Inc., division of F.H. Faulding Inc. Co. Ltd, 1538 Main North Road, Salisbury, South Australia, 5108 Australia.

Sincerely,

CAROLINA ABSORBENT COTTON COMPANY

Edwin O. Back
Director, Quality Assurance

EB:df

cc: Ms. Kristel Dean, Carolina Absorbent Cotton Company
Ms. Liz Reilly, Purepac Pharmaceutical Company

000020

SOLVAY POLYMERS

Quality Polymers Through Technology and People

May 24, 1995

Mr. Paul Chapman
Food and Drug Administration
Drug Master File Staff/CDR
Room 2-14
Park Bldg.
12420 Parklawn Drive
Rockville, MD 20852

RE: Drug Master File 3720

By copy of this letter, we are authorizing F. H. Faulding to incorporate by reference in any New Drug Application (NDA), and/or Abbreviated New Drug Application (ANDA), Solvay Polymers, Inc. Drug Master File 3720 on Fortilene® 1604 whenever Solvay Polymers, Inc. is considered as a supplier.

We authorize your office to review Solvay Polymers, Inc. DMF 3720 in support of the application or supplements submitted by F. H. Faulding.

The products supplied to F. H. Faulding will be manufactured in accordance with DMF 3720 and will comply with Good Manufacturing Practices.

We certify DMF 3720 is current; if changes are made to this DMF, F. H. Faulding will be notified and DMF 3720 will be amended.

Relevant information on Fortilene® 1604 is contained in Volume II of DMF 3720.

Please hold the information in DMF 3720 confidential to the extent possible under 21 CFR 314.430 of the New Drug and Antibiotic Regulations and 21 CFR 20.61 Public Information Regulations.

Yours truly,

Sam J. Valenti III

Vendor's Authorizing Official
Sam J. Valenti, III
Regulatory Coordinator

F. H. Faulding
200 Elmora Avenue
Elizabeth, NJ 07207
Attn: George Wagner

Customer File
REG-95-169

000021

Solvay Polymers, Inc. - Technical Center
1230 Battleground Road, Deer Park, Texas 77536 Mailing Address: P.O. Box 1000, Deer Park, Texas 77536-1000 1-800-338-0489 Fax: 713/476-3521

3802 Fairmont Parkway
P.O. Box 2006
Pasadena, Texas 77505-1195
Telephone 713 291 8700

Lyondell POLYMERS

May 3, 1995

Food and Drug Administration
Center for Drugs and Biologics
Drug Master File Staff
Central Document Room (Room 2-14)
Park Building
12420 Parklawn Drive
Rockville, MD 20852

RE: Drug Master File: 5036
Date of Submission: October 1, 1994 Update
Pages: 36, 37, and 38, PP 51B30V
Title: Type III; Lyondell Polypropylene Resins
Holder/Submitter: Lyondell Polymers Corporation

Attention DMF Staff:

Lyondell Polymers Corporation, P.O. Box 2006, Pasadena, TX 77505-1195, hereby authorizes the Food and Drug Administration to use the information contained in our Drug Master File for Lyondell Polypropylene Resin *PP 51B30V* when requested by FAULDING, Inc., 1538 Main North Road, Salisbury, South Australia, 5108, Australia, in behalf of any Notice of Claimed Investigational Exemption for a New Drug (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or supplement filed by FAULDING, Inc. Duplicate copies of our Drug Master File 5036 for Lyondell Polypropylene Resin *PP 51B30V* are on file with the FDA.

We warrant that the Lyondell Polypropylene Resin *PP 51B30V* to be furnished to FAULDING, Inc. will be manufactured as described in the Drug Master File 5036 and will meet the specifications therein.

It is requested that this data be maintained confidential to the Food and Drug Administration in accordance with 21 CFR Part 20 and Section 314.430 of the regulation of the Federal Food, Drug, and Cosmetic Act.

Sincerely yours,

Thomas L. Harder

Thomas L. Harder, C.S.P.
Product Safety Supervisor

TLH/eo

cc: DMF 5036/95 - B317.403
FAULDING, Inc.
Mold-Rite Plastics

H:\TLHARDER\WPDATA\95077.TLH

000022

VBC

Van Blarcom Closures, Inc.

156 Sanford Street
Brooklyn, N.Y. 11205
(718) 855-3810
Fax 718-935-9855

"Answering your needs in closures"

June 5, 1995

JUN 0 8 1995

Drug Master File Staff
FOOD AND DRUG ADMINISTRATION
Central Document Room (Room 2-14)
12420 Parklawn Drive
Rockville, MD 20852

RE: Drug Master File DMF #5828 - 33M/M, 38M/M, 45M/M AND 53M/M SAF-CAP I CHILD RESISTANT CLOSURE.

Dear Sir:

By copy of this letter, we are authorizing:

F.H. FAULDING
200 Elmora Avenue
Elizabeth, NJ 07207

to incorporate by reference in any New Drug Application (NDA), and/or Abbreviated New Drug Application (ANDA), Van Blarcom Closures Drug Master File #5828 on our 33m/m, 38m/m, 45m/m and 53m/m Saf-Cap I (all plastic) child resistant closures whenever Van Blarcom Closures is considered as a supplier.

We authorize your office to review Van Blarcom Closures DMF #5828 in support of the application or supplements submitted by F.H. FAULDING.

The products supplied to F.H. FAULDING will be manufactured in accordance with DMF #5828 and will comply with Good Manufacturing Practices.

We certify DMF #5828 is current; if changes are made to this DMF F.H. FAULDING will be notified and DMF #5828 will be amended.

Relevant information on our Saf-Cap I Child resistant Closure may be found in Section "F", pages 5, 6, 7, 8, and 10 Volume 1, re-submitted November 10, 1994. Pertinent information on the child resistant closures used may be found in this entire file.

000023

FOOD AND DRUG ADMINISTRATION June 5, 1995

Please hold the information in DMF #5828 confidential to the extent possible under 21 CRF 314.430 of the New Drug and Antibiotic Regulations and 21 CRF 20.61 Public Information Regulations.

Very truly yours,

VAN BLARCOM CLOSURES, INC.

John Scuderi

JOHN SCUDERI
SALES MANAGER

JS:lm
cc:
F.H. FAULDING
200 Elmora Avenue
Elizabeth, NJ 07207
Attn: George Wagner

000024

MOLD-RITE PLASTICS, INC.
1 PLANT STREET, P.O. BOX 160
PLATTSBURGH, NEW YORK 12901
(518) 561-1812

MAY 15 1995

April 27, 1995

Mr. Mark Matarese
Drug Master File Staff
Food & Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

RE: DRUG MASTER FILE 9775
MOLD-RITE PLASTICS, INC.
DATE OF SUBMISSION: JULY 8, 1992

Gentlemen:

This letter authorizes the Food & Drug Administration to refer to our Drug Master File 9775 on behalf of, and in support of any IND, NDA, or ANDA submitted by Faulding, Inc., Div. of F.H. Faulding & Co., Ltd., 1538 Main North Road, Salisbury S. Australia 5108, Australia.

The products referenced are manufactured with white Lyondell polypropylene and lined with PS22, & X-14 from Tekni-Plex, F-217 from Triseal, and SG75 from 3M as found on pages 74, 75, 79, 85, 86, 99, 100, & 108.

The information contained in our Drug Master File 9775, and all current and subsequent amendments thereto, is to be treated as **CONFIDENTIAL**, and not to be disclosed by the Food & Drug Administration to Faulding, Inc., or to any person outside the Food & Drug Administration without prior notification and written assent of Mold-Rite Plastics, Inc.

Sincerely,

Mold-Rite Plastics, Inc.

Paul Titherington
President

000025

3M Identification and Converter Systems Division
3M Center
St. Paul, MN 55144-1000
612 7[illegible]
800 2[illegible]

3M

May 2, 1995

Central Document Room
Food and Drug Administration
Park Building
12420 Parklawn Drive
Room 214
Rockville, MD 20857

Re: Safe-Gard Induction Innerseal #75M
Drug Master File 3782

To whom it may concern:

We are requesting that you open DMF 3782 for review of Safe-Gard Brand Induction Innerseal #75M for any IND, NDA, ANDA or supplemental NDA submitted by Faulding, Inc., Division of F.H. Faulding & Co., Inc.

Drug Master File 3782 was last amended for Safe-Gard #75M in April, 1994. Safe-Gard 75M will be manufactured in accordance with Good Manufacturing Practice. 3M will notify the customer of any formulation change.

Sincerely,

John E. Nordale
Senior Specialist, Regulatory Affairs
(612) 736-4221

jen
c: Faulding, Inc.
Div. of F.H. Faulding & Co., Inc.
1538 Main North Road
Salisbury, South Australia, 5108
Australia

Gary Titherington
Mold-Rite Plastics, Inc.
FAX: (518) 561-0017

000026

PACO PHARMACEUTICAL SERVICES, INC. | 1200 PACO WAY, Lakewood, New Jersey 08701 908 / 367-9000
FAX 908 / 364-5266

PACO

complete packaging and manufacturing services for the pharmaceutical and health care industries

February 2, 1995

Food and Drug Administration
Drug Master File Staff
Central Document Control Room
Park Building, Room 2-14
12420 Park Lawn Drive
Rockville, MD 20852

Re: Drug Master File No. (s) 3347 (Rev. 9/94)
Paco Packaging, Inc.
1200 Paco Way, Lakewood, NJ 08701

To Whom It May Concern:

We hereby authorize you to incorporate, by reference, said Master File in consideration of manufacturing and/or packaging the products (s) that are listed below (IND, NDA, ANDA), on behalf of the named firm.

FIRM: Faulding, Inc./A Division of F.H. Faulding & Co., LTD.
1538 Main North Road
Salisbury, S.A. 5108
Australia

PRODUCT (S): Any and All Products

Please refer to the specific section (s) of the Drug Master file (s) listed below in support of the aforementioned drug applications (s).

Title or Subject of DMF Document	Addendum	DMF page no. (s)
Drug Master File Type 1		In its entirety

We certify that the methods, facilities, and controls used for manufacturing and/or packaging are in conformity with current Good Manufacturing Practices set forth in 21 CFR 210 and 211.

We further certify that appropriate customers will be notified, prior to its implementation, of an essential change in Paco's operations.

Very truly yours,

Paul J. Siciliano
Director, Quality Assurance
and Regulatory Affairs

000027

PJS/lh/purepac/dmf3347-1

PGO

KLÖCKNER
PENTAPLAST

KLOCKNER PENTAPLAST OF AMER CA INC
P.O. Box 500 • Klockner Road
Gordonsville, VA 22942 USA

Phone: 703-832-3600
Fax: 703-832-5656

January 17, 1995

Food and Drug Administration
Center for Drugs and Evaluation & Research
Central Documents Room
Room 214
12420 Parklawn Drive
Rockville, MD 20857

RE: Type III Drug Master File No. 3764 Rigid PVC Sheet Marketed as Pentapharm

Dear FDA Reviewer:

The purpose of this letter is to provide authorization for FDA to refer to the Type III Drug Master File for Klöckner Pentaplast's rigid PVC Sheet (Pentapharm) in reviewing any claimed notice of Investigational Exemption of a New Drug (IND) or for a New Animal Drug (IAND), New Drug Applications (NDA), New Animal Drug Applications (NADA), Abbreviated New Drug Applications (ANDA) and any supplements or amendments thereto submitted by:

Faulding, Inc.
A Division of F. H. Faulding & Co., Ltd.
1538 Main North Road
Salisbury SA 5108
Australia

They will be using our type PA 33C/02. Information on this type can be found in submission dated April 25, 1994. Our DMF has been updated within the last year.

We certify that all material used in the Production of our sheet meet the appropriate Food Additive Regulations and that the material will be produced in compliance with Title 21 CFR Part 211 - Good Manufacturing Practices.

Very truly yours,

H O Sargent

H. O. Sargent
Laboratory Manager

HOS:cbt

cc: John Christoffersen - Purepac

000028

REYNOLDS METALS COMPANY

Flexible Packaging Division • Technology Center
2101 Reymet Road • Richmond, Virginia 23237-3768 • (804)281-2000

January 23, 1995

Central Document Room
Food and Drug Administration
Center for Drugs and Biologics
12420 Parklawn Drive
Room 214, Park Building
Rockville, MD 20852

Reference: Type III Drug Master File #984
Amendment: #13
Filing Dates: December 9, 1994

Dear Sir:

Information on Reynolds' Drug Pak 257 has been placed in a Confidential New Drug Master File in anticipation of the potential use of this material for drug packaging. Please refer to the above listed amendment and filing date in place of page numbers. Future dated amendments may be found in the latest table of contents.

Subject to the conditions stated in Section 314.420 of your regulations:

1. We hereby authorize you to refer to it in considering the new drug status of any product and in considering any new drug application or IND, or supplemental NDA.

2. We hereby authorize Faulding Inc., A Division of Faulding & Co., Ltd, Salisbury, SA 5108 Australia to ask you to refer to it in considering the new drug status of their products, and

3. We hereby authorize Faulding Inc., A Division of Faulding & Co., Ltd, Salisbury, SA 5108 Australia to incorporate it by reference in any new drug application or IND, or supplemental NDA.

The above product will be manufactured in accordance with Drug Master File 984 and the referenced amendment and filing date and in compliance with current good manufacturing practices. No changes will be made to this product without amendment to our Drug Master File 984 and notification of our customers.

Very truly yours,

Merle S. Kahn, Ph.D.
Manager, Regulatory Affairs

cc: John Christofferson - Purepac Pharmaceutical Co.

000029

Chevron

Chevron Chemical Company
P.O. Box 7400
Orange, TX 77631-7400

E. B. Parker, Ph.D.
Manager, Product Compliance
Technology Department
Phone 409 882 6160
Fax 409 882 6135

May 9, 1995

FOOD AND DRUG ADMINISTRATION
National Center for Drugs and Biologics
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

RE: DRUG MASTER FILE NO. 1572

Gentlemen:

Chevron Chemical Company hereby authorizes the Administration to refer to Drug Master File No. 1572 with regard to our polyethylene resin PE 5654 with respect to all new and supplemental new drug applications filed by F. H. Faulding, LTD of Elizabeth, NJ.

Listed below are all the submission dates, volume and page numbers for PE 5654:

Volume 2 February 8, 1995 Pages 160 - 161

Please hold the information in DMF 1572 confidential to the extent possible under 21 CFR 314.430 for the New Drug and Antibiotic Regulations and 21 CFR 20.61 Public Information Regulations.

Yours truly,

E. B. Parker

EBP/crs

cc: Jeanene Toth - Armin
Liz Reilly - F. H. Faulding, LTD

212-95.FDA V2-1572.170

000030

EASTMAN

Eastman Chemical Company
P. O. Box 1994
Kingsport, Tennessee 37662

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

May 5, 1995

Food and Drug Administration
Center for Drugs and Biologics
Central Document Room
Room 2-14
12420 Parklawn Drive
Rockville, MD 20852

Ladies and Gentlemen:

SUBJECT: DMF 9522 for "TENITE" Polyethylene E6838-975F

One of our customers, Armin Corporation, Jersey City, NJ, wishes to use our "TENITE" Polyethylene E6838-975F in a medical or pharmaceutical application for their customer, F. H. Faulding Company, Ltd.

On January 20, 1992, we sent the Administration a Type I drug master file for our polyethylene production facility and received your acknowledgement letter dated February 13, 1992. We now authorize reference to DMF 9522 in support of any application which Armin Plastics or F. H. Faulding Company has submitted or will submit. We regard the information in our master file as confidential and trade secret.

Composition information on "TENITE" Polyethylene E6838-975F is enclosed. Our composition information on this product is confidential information referred to in Section 1905 of Title 18 of the United States Code Annotated and is exempt from disclosure under Section 552b(c)(4) of Title 5 of the United States Code Annotated and Part 20, Subpart D of Title 21 of the Code of Federal Regulations.

Please direct any questions on the above product to me, Eastman Chemical Company, P. O. Box 1994, Kingsport, TN 37662 (615-229-3112).

Yours very truly,

Angela R Kinkead

Angela R. Kinkead
HSE Assistant

Enclosure

cc: Ms. Janeen Toth
Armin Plastics
301 West Side Avenue
Jersey City, NJ 07305
(No Enclosure)

F. H. Faulding Company, Ltd.
200 Elmora Avenue
Elizabeth, NJ 07207
(No Enclosure)

Note to Armin Plastics and F. H. Faulding Company, Ltd. : Eastman Chemical Company reserves the right at any time or times to make changes in the composition of our products, including the product described herein, or to discontinue the manufacture of any such product. However, in the event of any change in the composition of this product, we will advise you of such change prior to any shipment containing the product with changed composition. We shall have no other or further obligation in this respect.

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National Quality Award 1993 Winner
Eastman Chemical Company

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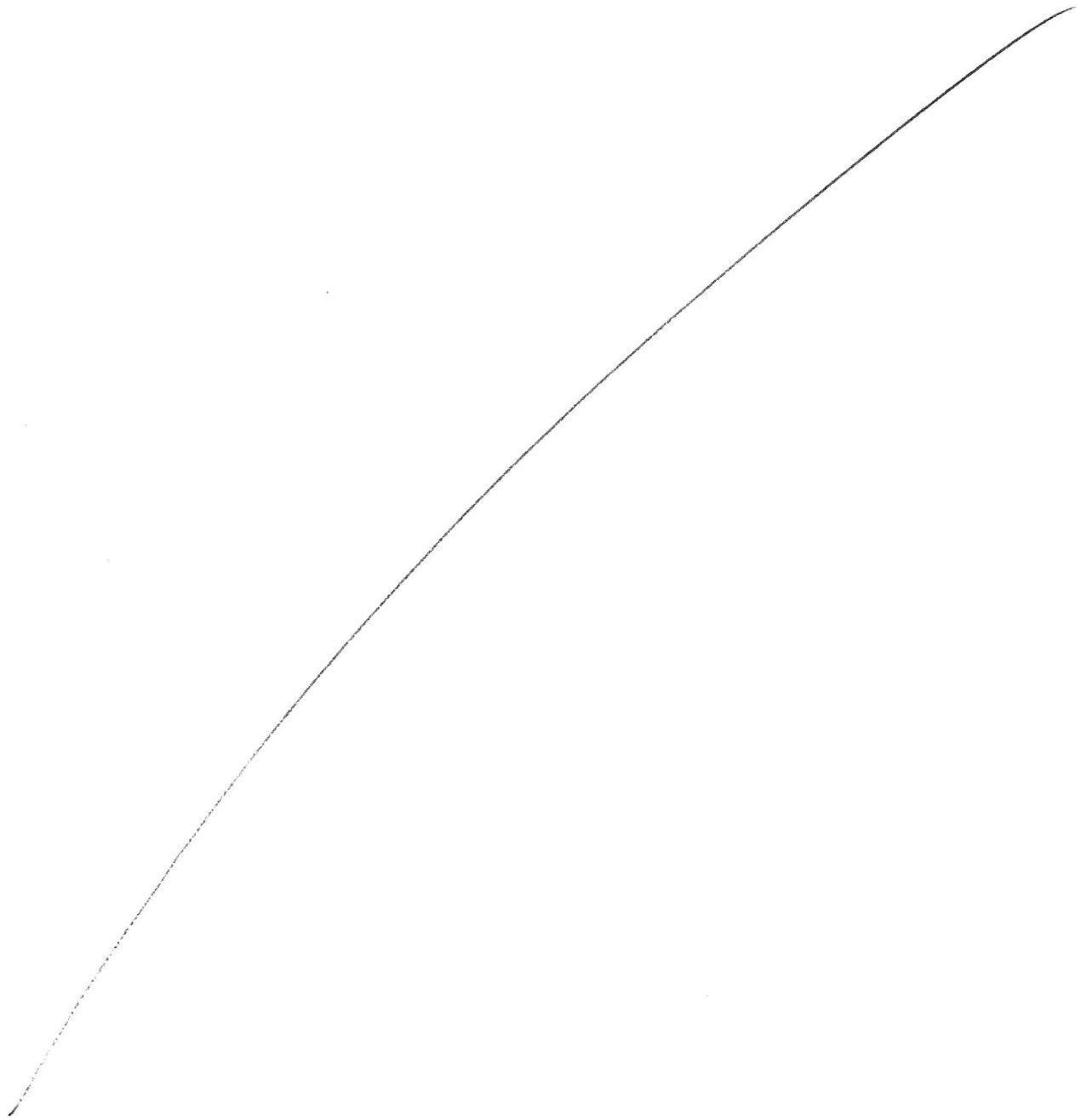
Item	Description	Volume	Page



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Item	Description	Volume	Page
12	**Case Report Forms** CRFs for each patient who died during a clinical study or who did not complete the study because of an adverse event		

Study	Patient Id.	AE / Death	Responsible Investigator		
CDD-14785 (cont'd)	06-LDM	AE	Croghan	175	166
	07-ISG	death	Croghan	175	223
	08-RMC	AE	Croghan	176	001
	01-RKM	AE	D'Errico	176	056
	06-IMR	AE	D'Errico	176	128
	02-FGA	death	Eisenberg	176	189
	01-DMH	death	Fintel	176	240
	02-RIW	AE	Fintel	177	001
	01-BK	AE	George	177	058
	01-AF	AE	Glover	177	148
	01-JKS	death	Hansen	177	198
	04-DHO	death	Hansen	177	230
	01-MLB	AE	Homesly	177	286
	01-EM	death	Kerr	178	001
	02-SKC	AE	Kerr	178	060
	03-SVM	death	Kerr	178	107
	04-MKP	AE	Kerr	178	156
	05-MHB	death	Kerr	178	231
	06-CEC	AE	Kerr	178	287
	08-VMS	AE	Kerr	179	001
	16-SAB	AE	Kerr	179	062
	17-MRB	death	Kerr	179	109
	19-RV	death	Kerr	179	162
	21-ECH	AE	Kerr	179	218
	22-MF	death	Kerr	179	278
	23-DFW	death	Kerr	180	001
	01-DLS	death	Kuenn	180	057
	02-OLY	death	Lamon	180	112
	04-RS	AE	Lamon	180	176
	02-RHD	AE	Lester	180	234
	01-JD	death	MacDonald	181	001
	01-IIP	AE	Moran	181	054
	04-JHR	death	Moran	181	099
	01-VA	AE	Mullane	181	156
	03-MW	death	Mullane	181	186
	04-MS	AE	Mullane	181	236
	06-JJ	AE	Mullane	182	001
	02-BBG	death	Pineda	182	048

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Item	Description	Volume	Page
12	**Case Report Forms** CRFs for each patient who died during a clinical study or who did not complete the study because of an adverse event		

Study	Patient Id.	AE / Death	Responsible Investigator		
CDD-14785 (cont'd)	04-LMH	death	Pineda	182	100
	06-JMS	death	Pineda	182	161
	02-CAM	death	Pipoly	182	227
	01-YCJ	death	Roberts	182	272
	03-RLR	AE	Roberts	183	001
	04-EEM	death	Roberts	183	046
	05-MM	death	Roberts	183	099
	08-FLP	death	Roberts	183	148
	10-GWG	death	Roberts	183	201
	11-JLT	AE	Roberts	184	001
	12-CKC	death	Roberts	184	052
	13-JER	death	Roberts	184	099
	14-WRM	death	Roberts	184	151
	16-JMP	death	Roberts	184	208
	17-WBE	death	Roberts	184	259
	18-MNM	AE	Roberts	185	001
	22-IMM	death	Roberts	185	048
	23-JRS	AE	Roberts	185	098
	25-FMK	death	Roberts	185	142
	26-AA	death	Roberts	185	191
	28-EW	AE	Roberts	185	240
	29-FJH	AE	Roberts	186	001
	01-FR	AE	Sandler	186	050
	03-WAU	death	Sandler	186	102
	05-CPB	AE	Sandler	186	155
	01-RWC	death	Sarker	186	209
	02-PRB	death	Silberstein	186	257
	03-BKR	AE	Silberstein	187	001
	04-WEH	death	Silberstein	187	063
	05-JHM	death	Silberstein	187	116
	07-CFA	death	Silberstein	187	167
	08-KDH	AE	Silberstein	187	216
	09-HJA	AE	Silberstein	187	270
	12-ALR	death	Silberstein	188	001
	13-WBG	AE	Silberstein	188	049
	01-IP	death	Sooijan	188	113
	02-HD	death	Tester	188	160
	07-RV	death	Tester	188	210

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APPLICATION SUMMARY

INTRODUCTION

This summary, as required under 21 CFR 314.50(c), integrates all of the information included in this application.

KADIAN™ morphine sulfate sustained-release capsules have been developed by F. H. Faulding & Co. Limited, an Australian pharmaceutical company, and are designed to provide a true sustained-release oral morphine formulation for once-a-day or twice-a-day administration in the management of pain where treatment with opioid analgesics is required over a period of more than a few days.

KADIAN™ capsules consist of cores acting as drug reservoirs surrounded by a dissolution rate controlling polymer membrane. The polymer coated cores (or pellets) are encapsulated into hard gelatin capsules in three dosage strengths: 20 mg, 50 mg and 100 mg.

Throughout its development, KADIAN™ has been referred to by several different names. The product's early project code name was MOLLY. The product has also been referred to as KAPANOL® which is its trade name in other regions. In addition, KADIAN™ has been designated as "Morphine Sulfate Extended-Release Capsules" by Purepac Pharmaceutical Co. of Elizabeth, New Jersey, the US contract manufacturer of KADIAN™.

All of these names have been used at various times throughout this application and all refer to the same product.

Finally, note that Faulding Inc., the US sponsor of this application is a wholly owned subsidiary of Faulding and that Purepac Pharmaceutical Co., the US contract manufacturer, is a majority owned and controlled subsidiary of Faulding.

Annotated proposed labeling follows.

APPLICATION SUMMARY

1. PROPOSED TEXT OF LABELING FOR KADIAN™ - ANNOTATED

Cross-Reference

Chemistry,Manufacturing, & Control
(Vol. 2)

Faulding Proposed U.S. Labeling for Kadian™

KADIAN™
Morphine Sulfate Sustained-release

CII

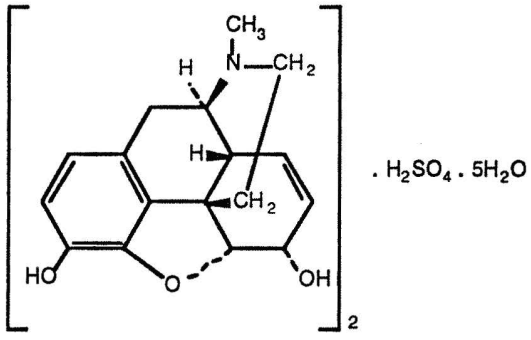
KADIAN™ 20 mg Capsules
KADIAN™ 50 mg Capsules
KADIAN™ 100 mg Capsules

Warning: May be habit forming

DESCRIPTION

KADIAN capsules 20, 50 and 100 mg contain polymer coated sustained-release pellets of the narcotic analgesic morphine sulfate for oral administration.

Chemically, morphine sulfate is 7,8-didehydro-4,5∝-epoxy-17-methyl-morphinan-3,6∝-diol sulfate (2:1) (salt) pentahydrate and has the following structural formula:



Morphine sulfate is an odourless, white, crystalline powder with a bitter taste and a molecular weight of 758 (as the sulfate). It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol:water partition coefficient of morphine is 1.42 at physiologic pH and the pK_b of 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4).

Each KADIAN Sustained-release Capsule contains either 20, 50 or 100 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: Hydroxypropyl Methylcellulose, Ethylcellulose, Methacrylic Acid Copolymer, Polyethylene Glycol, Diethyl Phthalate, Talc, Dye Black S-1-8090, Corn Starch and Sucrose.

Clin. Pharm. (Vol. 59)

CLINICAL PHARMACOLOGY

Morphine is a natural product that is the prototype for the class of natural and synthetic opioid (narcotic) analgesics. Opioids produce a wide spectrum of pharmacologic effects including analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release and physical dependence.

Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors (μ,δ,κ) located throughout the body. Morphine acts as a pure agonist, binding with and activating the μ-opioid receptor at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

Clin. Pharm. (Vol. 59)

Effects on the Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation and alterations of mood. Opiates of this class do not usually eliminate pain, but they do alter the effects of pain on the central nervous system resulting in a reduced perception of suffering.

Morphine produces respiratory depression by direct action on brain stem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension (or to direct electrical stimulation).

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine causes miosis, even in total darkness, and little tolerance develops to this effect. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g. pontine lesions of hemorrhagic or ischemic origins may produce similar findings). In overdose, marked mydriasis rather than miosis may be seen with severe hypoxia.

Clin. Pharm. (Vol. 59)

Effects on the Gastrointestinal Tract

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of sphincter of Oddi.

Clin. Pharm. (Vol. 59)

Effects on the Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to narcotic induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating.

Clin. Pharm. (Vol. 59)

Pharmacodynamics

The relationship between the blood level of morphine and the analgesic response will depend on the the patient's age, state of health, medical condition, and the extent of previous opioid treatment. For any given individual patient, effective analgesia will not occur below some minimum blood level, and adverse effects on mentation or respiration will become unacceptable above some maximum blood level.

For opioid-naive postoperative patients who are otherwise in good health the minimum morphine plasma level for analgesia ranges from 10-50 ng/mL, corresponding to the range of blood levels expected after a single intra-muscular dose of 5-10 mg. The toxic dose in this setting varies widely, ranging from a low of 10-15 mg in the elderly vulnerable patient up to doses of 30-50 mg tolerated by healthy volunteers.

For opioid-tolerant patients the situation is much more complex. Some patients will become rapidly tolerant to the analgesic effects of morphine, and will require high daily oral morphine doses for adequate pain control. Since the development of tolerance to both the therapeutic and adverse effects of opioids is highly individualized, the dose of morphine should be individualized to the patient's condition and should not be based on an arbitrary choice of a dose or blood level to be obtained.

HPB Sum (Vol. 26); **Clin. Pharm.** (Vol. 59)

KAP-RRC/91/01, (Vol. 41) **MOBU-7/90-2** (Vol. 34)

Pharmacokinetics

Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same for immediate or sustained-release formulations, although the time to peak blood level (T_{max}) will be longer and the C_{max} will be lower for formulations that delay the release of morphine to the gastrointestinal tract. KADIAN capsules contain polymer coated sustained-release pellets of morphine sulfate that release morphine significantly more slowly than from morphine sulfate tablets and other controlled-release oral preparations.

Because of pre-systemic elimination only about 20-40% of the administered dose reaches the central compartment. Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. Morphine also crosses the placental membranes and has been found in breast milk. About 30-35% of morphine is reversibly protein bound.

Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites including morphine-3-glucuronide and morphine-6-glucuronide.

MOB1/90, (Vol. 27) **MOBU7/90-2** (Vol. 34)

The glucuronide system has a very high capacity and is not easily saturated even in disease. Studies in healthy subjects and cancer patients have shown that the glucuronide metabolite to morphine mean molar ratios (based on AUC) are similar for both single doses and at steady state for KADIAN, controlled-release morphine sulfate tablets and morphine sulfate solution. The morphine to morphine-3-glucuronide to morphine-6-glucuronide mean molar ratios (based on AUC) are approximately 1:24:4.

MOBU7/90-2 (Vol. 34)

Morphine has a reported oral bioavailability of 20-40%, a volume of distribution (V_d) of 2-4 liters/kg, a clearance of 0.9-1.2 liters/kg/hr, and a terminal elimination half-life of 2 to 4 hours. Following the administration of oral morphine solution, approximately fifty percent of the morphine that will ever reach the central compartment intact, reaches it within 30 minutes. Following the administration of an equal amount of KADIAN to healthy volunteers, however, this extent of absorption occurs, on average, after 8 hours. While concurrent administration of food slows the absorption of KADIAN slightly, the extent of absorption is not affected and KADIAN can be administered without regard to meals. When KADIAN is given on a fixed dosing regimen, steady state is achieved in about two days.

MOBU7/90-2 (Vol. 34)

MOBU7/90-2 (Vol. 34), **HPB Sum.** (Vol. 26)

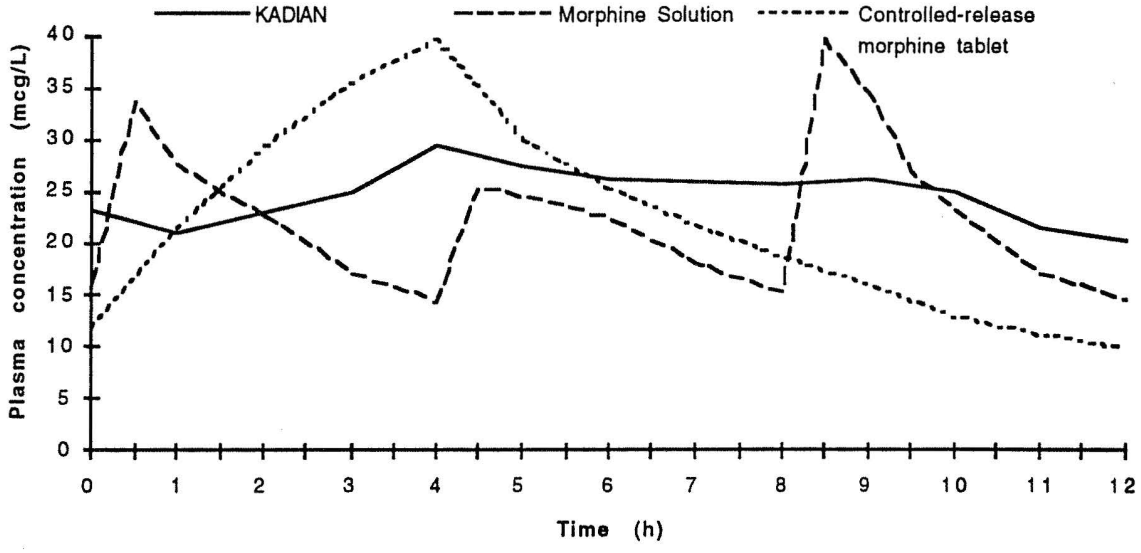
MOB1/90 (Vol. 27)

For any fixed dose and dosing interval, KADIAN will have at steady state a significantly lower C_{max} and a higher C_{min} than oral morphine solution and other controlled-release preparations (see graph below), but will be therapeutically similar with regard to pain control and adverse events.

MOBES8/90, (Vol. 86) **CDD-14556,** (Vol. 60) **MOR-9/92** (Vol. 77)

MOB1/90 (Vol. 27)

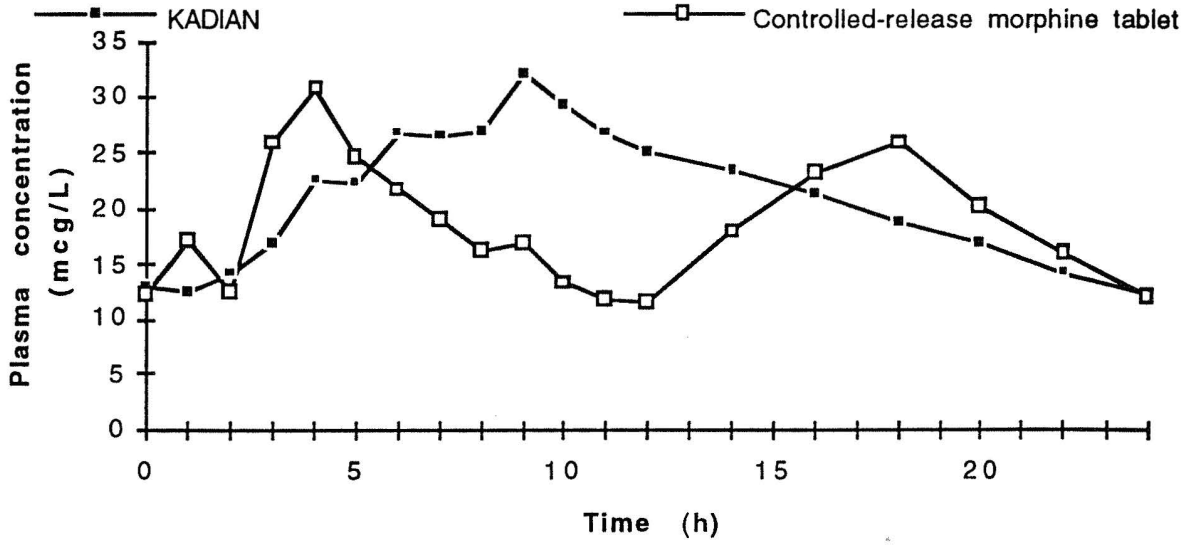
Mean steady state plasma morphine concentrations for KADIAN™ 50 mg (every 12 hours), controlled-release morphine tablet 50 mg (every 12 hours) and oral morphine solution 1 6.7 mg (every 4 hours); plasma concentrations were dose normalised.



MOR-9/92 (Vol. 77)

When given once-daily (every 24 hours) KADIAN will have at steady state a similar C_{max} and C_{min} when compared to twice-daily (every 12 hours) controlled-release morphine tablet (see graph below).

Mean steady state plasma morphine concentrations for KADIAN™ 100 mg (every 24 hours), controlled-release morphine tablet 50 mg (every 12 hours); plasma concentrations were dose normalised.



Morphine is converted to the active metabolite morphine-6-glucuronide. As accumulation of this metabolite has been demonstrated in patients with impaired renal function, caution should be exercised in patients with renal disease. While the glucuronidation pathway is intact even in cases of severe hepatic dysfunction, as with any drug, caution should be taken to adjust the dose to guard against unanticipated accumulation if renal and/or hepatic function is known to be seriously impaired.

Clinical Studies

ISS (Vol. 101)
ISS (Vol. 101)
ISE (Vol. 100)

A total of 177 healthy subjects and 337 patients with cancer pain participated in a total of 17 studies (11 pharmacokinetic and 6 clinical). Of these individuals, 158 healthy subjects and 268 patients received KADIAN. In the controlled clinical studies patients were followed for a median duration of 7±1 days and in the uncontrolled clinical studies patients were followed for a median duration of 103 days and up to 24 months. KADIAN was compared to oral morphine solution, MST Continus®, and MS Contin® using trial designs that followed the clinical and pharmacokinetic performance of each treatment in cancer patients receiving chronic opioid therapy.

CDD-14556, (Vol. 60) **MOR-9/92** (Vol. 77)
ISE (Vol. 100)

At the time of submission 110 patients had received KADIAN administered once-a-day (every 24 hours). In two controlled trials patients were titrated to a stable 24-hour morphine requirement, KADIAN administered every 24 hours to 78 evaluable patients provided similar analgesia to the same amount of morphine given as MS Contin® every 12 hours.

Individualization of Dosage

The best use of opioid analgesics in the management of chronic malignant and non-malignant pain is challenging, and is well described in materials published by the World Health Organization and the Agency for Health Care Policy and Research which are available from the manufacturer upon request. KADIAN is a third step drug which is most useful when the patient requires a constant level of opioid analgesia as a "floor" or "platform" from which to manage breakthrough pain. When a patient has reached the point where comfort cannot be provided with a combination of non-narcotic medications (NSAIDs & acetaminophen) and intermittent use of moderate or strong opioids, the patient's total opioid therapy should be converted into a 24 hour oral morphine equivalent.

CDD-14556 (Vol. 60), **CDD-14922** (Vol. 76)
MOBES8/90 (Vol. 86), **MOR-5/92** (Vol. 92)

KADIAN should be started by administering one-half of the total daily oral morphine dose as KADIAN capsules every 12 hours (twice-a-day) **or** by administering the total daily oral morphine dose as KADIAN capsules every 24 hours (once-a-day). The dose should be titrated no more frequently than every-other-day to allow the patients to stabilise before escalating the dose. If breakthrough pain occurs, the dose may be supplemented with a small dose (less than 20% of the total daily dose) of an immediate-release product. Patients who are excessively sedated after a once-a-day dose or who regularly experience inadequate analgesia before the next dose should be switched to twice-a-day dosing.

CDD-14556 (Vol. 60), **CDD-14922** (Vol. 76),
MOR-5/92 (Vol. 92), **MOR-9/92** (Vol. 77)

Only the 20 mg strength should be started in patients who do not have a proven tolerance to opiates, and usually should be advanced at a rate not greater than 20 mg every-other-day. Most patients will rapidly develop some degree of tolerance, requiring dosage adjustment until they have achieved their individual best balance between baseline analgesia and opioid side effects such as confusion, sedation and constipation. No guidance can be given as to the recommended maximal dose, especially in patients with chronic pain of malignancy. In such cases the total dose of KADIAN should be advanced until the desired therapeutic endpoint is reached or clinically significant opioid-related adverse reactions intervene.

ISE (Vol. 100)

INDICATIONS AND USAGE

KADIAN is indicated for the management of pain where treatment with an opioid analgesic is indicated for more than a few days.

KADIAN was developed for use in patients with chronic pain who require repeated dosing with a potent opioid analgesic, and has been tested in patients with pain due to a variety of malignant conditions. KADIAN has not been tested as an analgesic for the treatment of acute pain or in the postoperative setting and is not recommended for such use.

CONTRAINDICATIONS

KADIAN is contraindicated in patients with a known hypersensitivity to morphine, morphine salts or any of the capsule components.

WARNINGS

(See also: CLINICAL PHARMACOLOGY)

Impaired Respiration

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs more frequently in elderly and debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction when even moderate therapeutic doses may significantly decrease pulmonary ventilation.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increases in pressure in patients with head injuries. Morphine should only be administered under such circumstances when considered essential and then with extreme care.

Hypotensive Effect

KADIAN, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a reduced blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics. (See also:PRECAUTIONS: Drug Interactions.) KADIAN may produce orthostatic hypotension in ambulatory patients.

KADIAN, like all opioid analgesics, should be administered with caution to patients in circulatory shock, as vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Gastrointestinal Obstruction

KADIAN should not be given to patients with gastrointestinal obstruction particularly paralytic ileus as there is a risk of the product remaining in the stomach for an extended period and the subsequent release of a bolus of morphine when normal gut motility is restored. As with other solid morphine formulations diarrhea may reduce morphine absorption.

ISS (Vol. 101); **Clin. Pharm.** (Vol. 59)

PRECAUTIONS

(See also: CLINICAL PHARMACOLOGY)

General

KADIAN is intended for use in patients who require continuous treatment with a potent opioid analgesic. As with any potent opioid, it is critical to adjust the dosing regimen for KADIAN for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of the initial dose of KADIAN, attention should be given to the points under DOSAGE AND ADMINISTRATION.

Cordotomy

Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive KADIAN within 24 hours of the procedure. In addition, the post-procedure titration of analgesics for such patients should be individualized to avoid either oversedation or withdrawal syndromes.

Special risk groups

KADIAN should be administered with caution, and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; patients with Addison's disease; myxodema; hypothyroidism; prostatic hypertrophy or urethral stricture.

Caution should also be exercised in the administration of KADIAN to patients with CNS depression; toxic psychosis; acute alcoholism or delirium tremens; severe kyphoscoliosis; convulsive disorders; patients about to undergo biliary surgery and patients with acute pancreatitis secondary to biliary tract disease.

Driving and operating machinery

Morphine may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Patients must be cautioned accordingly. Patients should also be warned about the potential combined effects of morphine with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol (see: Drug Interactions).

Information for Patients
If clinically advisable, patients receiving KADIAN should be given the following instructions by the physician:

1. The dose of KADIAN should not be adjusted without consulting the physician.

2. Morphine may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g. driving, operating machinery).
Patients starting KADIAN should be advised not to engage in hazardous activities until they have established that they can maintain normal alertness.

3. Morphine should not be taken with alcohol or other CNS depressants (sleeping medication, tranquilizers) because additive effects including CNS depression may occur. A physician should be consulted if other prescription medications are currently being used or are prescribed for future use.

4. For women of childbearing potential who become or are planning to become pregnant, a physician should be consulted.

5. **The pellets in KADIAN capsules should NOT be chewed, crushed or dissolved.**

Drug Interactions

CNS Depressants: Morphine should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, phenothiazines, other tranquilizers and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. When such combined therapy is contemplated, the initial dose of one or both agents should be reduced by at least 50%.

Muscle Relaxants: Morphine may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression.

Mixed Agonist/Antagonist Opioid Analgesics: From a theoretical perspective, mixed agonist/antagonist analgesics (i.e. pentazocine, nalbuphine and butorphanol) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs can intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion and significant depression of respiration, sometimes leading to coma. Morphine should not be given to patients taking MAOIs or within 14 days of stopping such treatment.

Cimetidine: There is a report of confusion and severe respiratory depression when a hemodialysis patient was administered morphine and cimetidine.

Diuretics: Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

MOBU7/90-2 (Vol. 34)

Food: The bioavailability of KADIAN is not significantly affected by food.

Non-Clin. Pharm. & Tox. (Vol. 22)

Carcinogenicity/Mutagenicity/Impairment of Fertility

Studies of morphine sulfate in animals to evaluate the drug's carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

ISS (Vol. 101)

Pregnancy

Teratogenic effects - CATEGORY C: Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is no clearly defined risk, such experience can not exclude the possibility of infrequent or subtle damage to the human fetus.

KADIAN should be used in pregnant women only when the perceived need outweighs the known risks.

Nonteratogenic effects: Infants born to mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

ISS (Vol. 101)

Labour and Delivery

KADIAN is not recommended for use in women during and immediately prior to labor, where shorter acting analgesics are more appropriate. Infants born to mothers receiving opioid analgesics during labour should be observed closely for signs of respiratory depression. In such infants, a specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression.

ISS (Vol. 101)

Nursing Mothers

Low levels of morphine sulfate have been detected in human milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Nursing should not be undertaken while a patient is receiving KADIAN since morphine may be excreted in the milk.

Pediatric Use

KADIAN has not been evaluated in children.

ISS (Vol. 101)

ADVERSE REACTIONS

The adverse reactions caused by morphine are essentially the same as those observed with other oral and parenteral opioid analgesics. They include the following major hazards: respiratory depression, apnea and to a lesser degree; circulatory depression, respiratory arrest, shock and cardiac arrest.

More common adverse reactions that are due to the pharmacological activity of morphine are: constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria and euphoria.

Management of Excessive Sedation: Most patients receiving morphine will experience initial drowsiness. This usually disappears in three to five days and is not a cause of concern unless it is excessive, or accompanied with unsteadiness or confusion. Dizziness and unsteadiness may be associated with postural hypotension, particularly in elderly or debilitated patients.

Excessive or persistent sedation should be investigated. Factors to be considered should include: concurrent sedative medications, the presence of hepatic or renal insufficiency, hypoxia or hypercapnia due to exacerbated respiratory failure, intolerance to the dose used (especially in older patients), disease severity and the patient's general condition.

The dosage should be adjusted according to individual needs but because of reduced clearance and/or increased pharmacodynamic sensitivity, dosage may be lower in patients over 50 years of age compared to younger patients. If the dose of KADIAN is reduced and pain is not adequately controlled, the dose may be carefully increased every second day.

Management of nausea and vomiting: Nausea and vomiting is common after single doses of morphine or as an early undesirable effect of regular opioid therapy. The prescription of a suitable antiemetic should be considered. The frequency of nausea and vomiting usually decreases within a week or so but may persist due to opioid-induced gastric stasis. Metoclopramide is often useful in such patients.

Management of constipation: Virtually all patients suffer from constipation while taking opioids on a chronic basis. Some patients, particularly elderly, debilitated or bedridden patients may become impacted. Patients must be cautioned accordingly and laxatives, softeners and other appropriate treatments should be initiated from the beginning of opioid therapy.

Other Less Common Adverse Effects include:

Central Nervous System: Euphoria, dysphoria, weakness, and occasional hallucinations.

Gastrointestinal: Dry mouth, anorexia, colic, taste alterations and biliary colic.

Cardiovascular: Flushing of the face, chills, tachycardia, bradycardia, palpitations, hypotension and hypertension.

Genitourinary: Urine retention or hesitancy, reduced libido or reduced potency.

Dermatologic: Pruritus, urticaria, other skin rashes, edema and diaphoresis.

Endocrine: A syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatremia secondary to decreased free-water excretion.

Visual Disturbances: Blurred vision, nystagmus, diplopia and miosis.

Drug Abuse Liability Ass. (Vol. 103)

DRUG ABUSE AND DEPENDENCE

Morphine is the prototype of opioid agonist drugs, and may be subject to misuse, abuse and addiction. Addiction to opiates prescribed for pain management is rare, but requests for opiates from patients addicted to opioids is common and physicians should take appropriate care in prescribing this controlled substance.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with narcotic antagonist activity, e.g. naloxone or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine; See also OVERDOSAGE).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued narcotic usage. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

In chronic pain patients, and in narcotic-tolerant cancer patients, the administration of KADIAN should be guided by the degree of tolerance manifested. Physical dependence, per se, is not ordinarily a concern when one is dealing with a patient in pain, and fear of tolerance should not deter using adequate doses to adequately relieve pain.

If morphine is abruptly discontinued, a moderate to severe abstinence syndrome may occur. This is usually mild and is characterized by rhinitis, myalgia, abdominal cramping and occasional diarrhea. Most observable symptoms disappear in 5-14 days without treatment; however, there may be a phase of secondary or chronic abstinence which may last for 2-6 months characterized by insomnia, irritability and muscular aches.

If treatment of physical dependence of patients taking morphine is necessary, the patient may be detoxified by gradual reduction of the dosage. Gastrointestinal disturbances or dehydration should be treated accordingly.

OVERDOSAGE

Symptoms

Acute overdosage with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, bradycardia and hypotension.

Treatment

Primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a sustained-release formulation such as KADIAN has been taken. Care should be taken to secure the airway before attempting treatment by gastric emptying or activated charcoal.

The pure opioid antagonist, naloxone, is a specific antidote against respiratory depression which results from opioid overdose. Naloxone (usually 0.4 to 2.0 mg) should be administered intravenously; however, because its duration of action is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. KADIAN will continue to release and add to the morphine load for up to 12 hours after administration and the management of morphine overdose should be monitored accordingly. If the response to naloxone is suboptimal or not sustained, additional naloxone may be re-administered, as needed, or given by continuous infusion to maintain alertness and respiratory function.

MOBU-7/90-2 (Vol. 34),
KAP-RRC/91/01 (Vol. 41),
MOBU9/90 (Vol. 56),
MOBU-10/90 (Vol. 50),
MOR-8/92 (Vol. 53)

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Naloxone should be administered cautiously to persons who are known, or suspected to be physically dependent on KADIAN. In such cases, an abrupt or complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

Opioid Tolerant individuals: In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of a narcotic antagonist in such a person should be reserved to cases where such treatment is clearly needed. If necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with care and by titration with smaller than usual doses of the antagonist.

Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

DOSAGE AND ADMINISTRATION

KADIAN CAPSULES SHOULD BE SWALLOWED WHOLE. THE CAPSULES AND PELLETS SHOULD NOT BE CHEWED, CRUSHED OR DISSOLVED.

TAKING BROKEN, CHEWED OR CRUSHED KADIAN CAPSULES WILL LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

ISE (Vol. 100), **MOBES8/90** (Vol. 86), **CDD-14556** (Vol. 60), **MOB1/90** (Vol. 27), **MOR-9/92** (Vol. 77)

The sustained-release nature of KADIAN allows it to be administered on a convenient once-a-day or twice-a-day schedule . KADIAN produces analgesia similar to conventional immediate-release and other controlled-release formulations with regard to pain control for the same total daily dose of morphine. However, peak and trough blood levels depend on the release characteristics of each specific formulation, and other oral morphines may not be therapeutically equivalent to KADIAN.

ISE (Vol. 100),**CDD-14556** (Vol.60), **MOR-9/92** (Vol.77), **MOBES8/90** (Vol. 86)

HPB Sum. (Vol. 26)

KAP-RRC/91/01 (Vol. 41), **MOB1/90** (Vol. 27), **MOR-9/92** (Vol. 77) **ISE** (Vol. 100); **Clin. Pharm.** (Vol. 59)

KADIAN capsules have the same extent of absorption (AUC) as immediate-release oral formulations and controlled-release oral formulations of morphine sulfate. However, key pharmacokinetic parameters (e.g., C_{max}, T_{max}) for KADIAN are significantly different to other controlled-release oral formulations so that they are not strictly bioequivalent to KADIAN.

MOB1/90 (Vol. 27), **KAP-RRC/91/01** (Vol. 41), **MOBU7/90-2** (Vol. 34) **HPB Sum.** (Vol. 26)

As with any potent opioid drug product, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of KADIAN, attention should be given to:

1) the total daily dose, potency and kind of opioid the patient has been taking previously;
2) the reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed;
3) the patient's degree of opioid tolerance;
4) the general condition and medical status of the patient;
5) concurrent medication;
6) the type and severity of the patient's pain.

The following dosing recommendations, therefore, can only be considered suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of an individual patient.

Conversion from Other Oral Morphine Formulations to KADIAN

CDD-14556 (Vol. 60), **CDD-14922** (Vol. 76), **MOBES8/90** (Vol. 86), **MOR-5/92** (Vol. 92) **ISE** (Vol. 100)

Patients on other oral morphine formulations may be converted to KADIAN by administering one-half of the patient's total daily oral morphine dose as KADIAN capsules every 12 hours (twice-a-day) **or** by administering the total daily oral morphine dose as KADIAN capsules every 24 hours (once-a-day). The dosing interval of KADIAN should not be reduced below every 12 hours.

ISE (Vol. 100), **CDD-14556**(Vol. 60), **CDD-14922** (Vol. 76), **MOR-5/92** (Vol. 92), **MOR-9/92** (Vol. 77)

Conversion from Parenteral Morphine or Other Parenteral or Oral Opioids to KADIAN

KADIAN can be administered as the initial oral morphine drug product. While there are useful tables of oral and parenteral equivalents in cancer analgesia, there is substantial interpatient variation in the relative potency of different opioid drugs and formulations. For these reasons, it is better to underestimate the patient's 24 hour oral morphine requirement and to have to increase the dose, than to overestimate and have to manage an adverse event. The following general points should be considered:

Parenteral to oral morphine ratio: Estimates of the oral to parenteral potency of morphine vary from 1:6 to 1:2 in chronic use. A dose of oral morphine three times the daily parenteral morphine requirement may be sufficient in chronic use settings.

Other parenteral or oral opioids to oral morphine sulfate: Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate (see Table 1 for oral opioid potency). In general, it is safest to give only half of the estimated daily morphine demand as the initial dose, and to deal with inadequate analgesia by supplementation with immediate-release morphine. (See discussion which follows.)

CDD-14556 (Vol. 60),
CDD-14922 (Vol. 76),
MOR-5/92 (Vol. 92), **MOR-9/92** (Vol. 77)
ISE (Vol. 100)

The first dose of KADIAN may be taken with the last dose of any immediate-release (short-acting) opioid medication due to the long T_{max} after administration of KADIAN.

Table 1: Approximate oral opioid potency ratios relative to oral morphine*

24 Hour Oral Dosage of Prior Opioid Dose		24 Hour Oral Morphine
Methadone**	1.0 mg	1.5 mg
Papaveratum	1.0 mg	1.5 mg
Oxycodone	1.0 mg	1.0 mg
Morphine solution	1.0 mg	1.0 mg
MS Contin®	1.0 mg	1.0 mg
Roxanol™	1.0 mg	1.0 mg

* Adapted from Twycross and Lack, (1989). Oral morphine in advanced cancer. 2nd ed. Beaconsfield

** Methadone has a prolonged and highly variable plasma half-life, which leads to cumulation when given repeatedly. This estimate is only an approximation for the first dose.

Use of KADIAN as the First Opioid Analgesic

There has been no evaluation of KADIAN as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient to adequate analgesia using a sustained-release morphine, it is ordinarily advisable to begin treatment using an immediate-release morphine formulation.

CDD-15220, CDD-14785, MOR-7/92, MOR-10/92

ISE (Vol. 100)
CDD-14556 (Vol. 60), **MOR-9/92** (Vol. 77)

HPB Sum. (Vol. 26), **MOBU7/90-2** (Vol. 34), **KAP-RRC/91/01** (Vol. 41)

Considerations in the Adjustment of Dosing Regimens

Whatever the approach, if signs of excessive opioid effects are observed early in the dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, 'breakthrough' pain occurs when KADIAN is administered on an every 24 hours dosing regimen, consideration should be given to dosing every 12 hours. If breakthrough pain occurs on an every 12 hours dosing regimen a supplemental dose of a short-acting analgesic may be given. As experience is gained, adjustments in both dose and dosing interval can be made to obtain an appropriate balance between pain relief and opioid side effects. To avoid accumulation the dosing interval of KADIAN should not be reduced below every 12 hours.

Conversion from KADIAN to other controlled-release oral morphine formulations

HPB Sum. (Vol. 26), **KAP-RRC/91/01** (Vol. 47), **MOB1/90** (Vol. 27)

KADIAN is not bioequivalent to other controlled-release morphine preparations. Although for a given dose the same total amount of morphine is available from KADIAN as from morphine solution or controlled-release morphine tablets, the slower release of morphine from KADIAN results in reduced maximum and increased minimum plasma morphine concentrations than with other products. Conversion from KADIAN to the same total daily dose of other controlled-release morphine preparations may lead to either excessive sedation at peak or inadequate analgesia at trough and close observation is recommended.

HPB Sum. (Vol. 26), **MOB1/90** (Vol. 27)

Conversion from KADIAN to parenteral opioids

When converting a patient from KADIAN to parenteral opioids, it is again best to select an initial dose of parenteral opioid that is about half the calculated value. For example, to estimate the required 24 hour dose of morphine for IM use, one would take the 24 hour oral morphine dose, divide by an oral to parenteral conversion ratio of 6:1, divide the estimated 24 hour parenteral demand by the number of doses (6 for a 4 hourly dosing regimen), then halve this dose as an initial trial.

For example, to estimate the required 24 hour dose of morphine for IM administration, use a conversion of 1 mg of morphine IM for every 6 mg of morphine as KADIAN. The IM 24 hour dose is then divided by 6 and administered 4 hourly.

This approach is likely to require a dosage increase in the first 24 hours for many patients, but is recommended because it is less likely to cause overdose than trying to establish an equivalent dose without titration.

Opioid analgesic agents may not effectively relieve dysesthetic pain, post-herpetic neuralgia, stabbing pains, activity-related pain, and some forms of headache. This does not mean that patients suffering from these types of pain should not be given an adequate trial of opioid analgesics. However, such patients may need to be promptly evaluated for other types of pain therapy.

Safety and Handling

KADIAN consists of closed hard gelatin capsules containing polymer coated morphine sulfate pellets that pose no known handling risk to health care workers. Oral morphine products are not known to be associated with a high risk of diversion, but all strong narcotics are liable to diversion and misuse both by the general public and health care workers, and should be handled accordingly.

HOW SUPPLIED

KADIAN capsules contain white to off-white or tan colored polymer coated sustained-release pellets of morphine sulfate and are available in three dose strengths:

20 mg size 4 capsule, clear cap imprinted 'K 20' and clear body imprinted with two black bands.

50 mg size 2 capsule, clear cap imprinted 'K 50' and clear body imprinted with three black bands.

100 mg size 0 capsule, clear cap imprinted 'K 100' and clear body imprinted with four black bands.'

Store capsules at controlled room temperature 15° to 30°C (59°-86°F). Protect from light and moisture.

Dispense in sealed, tamper-evident, childproof, light-resistant container.

CAUTION

DEA Order Form Required.

Federal law prohibits dispensing without prescription.

Revision date: June 22, 1995

000108

APPLICATION SUMMARY

1. PROPOSED TEXT OF LABELING FOR KADIAN™ - ANNOTATED

Cross-Reference

Faulding Proposed U.S. Labeling for Kadian™

KADIAN™
Morphine Sulfate Sustained-release

C II

KADIAN™ 20 mg Capsules
KADIAN™ 50 mg Capsules
KADIAN™ 100 mg Capsules

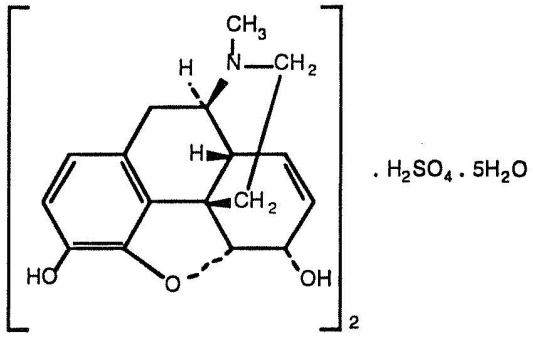
Warning: May be habit forming

Chemistry,Manufacturing, & Control
(Vol. 2)

DESCRIPTION

KADIAN capsules 20, 50 and 100 mg contain polymer coated sustained-release pellets of the narcotic analgesic morphine sulfate for oral administration.

Chemically, morphine sulfate is 7,8-didehydro-4,5∝-epoxy-17-methyl-morphinan-3,6∝-diol sulfate (2:1) (salt) pentahydrate and has the following structural formula:



Morphine sulfate is an odourless, white, crystalline powder with a bitter taste and a molecular weight of 758 (as the sulfate). It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol:water partition coefficient of morphine is 1.42 at physiologic pH and the pK_b of 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4).

Each KADIAN Sustained-release Capsule contains either 20, 50 or 100 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: Hydroxypropyl Methylcellulose, Ethylcellulose, Methacrylic Acid Copolymer, Polyethylene Glycol, Diethyl Phthalate, Talc, Dye Black S-1-8090, Corn Starch and Sucrose.

Clin. Pharm. (Vol. 59)

CLINICAL PHARMACOLOGY

Morphine is a natural product that is the prototype for the class of natural and synthetic opioid (narcotic) analgesics. Opioids produce a wide spectrum of pharmacologic effects including analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release and physical dependence.

Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors (μ,δ,κ) located throughout the body. Morphine acts as a pure agonist, binding with and activating the μ-opioid receptor at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

Clin. Pharm. (Vol. 59)

Effects on the Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation and alterations of mood. Opiates of this class do not usually eliminate pain, but they do alter the effects of pain on the central nervous system resulting in a reduced perception of suffering.

Morphine produces respiratory depression by direct action on brain stem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension (or to direct electrical stimulation).

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine causes miosis, even in total darkness, and little tolerance develops to this effect. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g. pontine lesions of hemorrhagic or ischemic origins may produce similar findings). In overdose, marked mydriasis rather than miosis may be seen with severe hypoxia.

Clin. Pharm. (Vol. 59)

Effects on the Gastrointestinal Tract

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of sphincter of Oddi.

Clin. Pharm. (Vol. 59)

Effects on the Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to narcotic induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating.

Clin. Pharm. (Vol. 59)

Pharmacodynamics

The relationship between the blood level of morphine and the analgesic response will depend on the the patient's age, state of health, medical condition, and the extent of previous opioid treatment. For any given individual patient, effective analgesia will not occur below some minimum blood level, and adverse effects on mentation or respiration will become unacceptable above some maximum blood level.

For opioid-naive postoperative patients who are otherwise in good health the minimum morphine plasma level for analgesia ranges from 10-50 ng/mL, corresponding to the range of blood levels expected after a single intra-muscular dose of 5-10 mg. The toxic dose in this setting varies widely, ranging from a low of 10-15 mg in the elderly vulnerable patient up to doses of 30-50 mg tolerated by healthy volunteers.

For opioid-tolerant patients the situation is much more complex. Some patients will become rapidly tolerant to the analgesic effects of morphine, and will require high daily oral morphine doses for adequate pain control. Since the development of tolerance to both the therapeutic and adverse effects of opioids is highly individualized, the dose of morphine should be individualized to the patient's condition and should not be based on an arbitrary choice of a dose or blood level to be obtained.

HPB Sum (Vol. 26); **Clin. Pharm.** (Vol. 59)

Pharmacokinetics

KAP-RRC/91/01, (Vol. 41) **MOBU-7/90-2** (Vol. 34)

Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same for immediate or sustained-release formulations, although the time to peak blood level (T_{max}) will be longer and the C_{max} will be lower for formulations that delay the release of morphine to the gastrointestinal tract. KADIAN capsules contain polymer coated sustained-release pellets of morphine sulfate that release morphine significantly more slowly than from morphine sulfate tablets and other controlled-release oral preparations.

Because of pre-systemic elimination only about 20-40% of the administered dose reaches the central compartment. Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. Morphine also crosses the placental membranes and has been found in breast milk. About 30-35% of morphine is reversibly protein bound.

Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites including morphine-3-glucuronide and morphine-6-glucuronide.

MOB1/90, (Vol. 27) **MOBU7/90-2** (Vol. 34)

The glucuronide system has a very high capacity and is not easily saturated even in disease. Studies in healthy subjects and cancer patients have shown that the glucuronide metabolite to morphine mean molar ratios (based on AUC) are similar for both single doses and at steady state for KADIAN, controlled-release morphine sulfate tablets and morphine sulfate solution. The morphine to morphine-3-glucuronide to morphine-6-glucuronide mean molar ratios (based on AUC) are approximately 1:24:4.

MOBU7/90-2 (Vol. 34)

Morphine has a reported oral bioavailability of 20-40%, a volume of distribution (V_d) of 2-4 liters/kg, a clearance of 0.9-1.2 liters/kg/hr, and a terminal elimination half-life of 2 to 4 hours. Following the administration of oral morphine solution, approximately fifty percent of the morphine that will ever reach the central compartment intact, reaches it within 30 minutes. Following the administration of an equal amount of KADIAN to healthy volunteers, however, this extent of absorption occurs, on average, after 8 hours. While concurrent administration of food slows the absorption of KADIAN slightly, the extent of absorption is not affected and KADIAN can be administered without regard to meals. When KADIAN is given on a fixed dosing regimen, steady state is achieved in about two days.

MOBU7/90-2 (Vol. 34), **HPB Sum.** (Vol. 26)

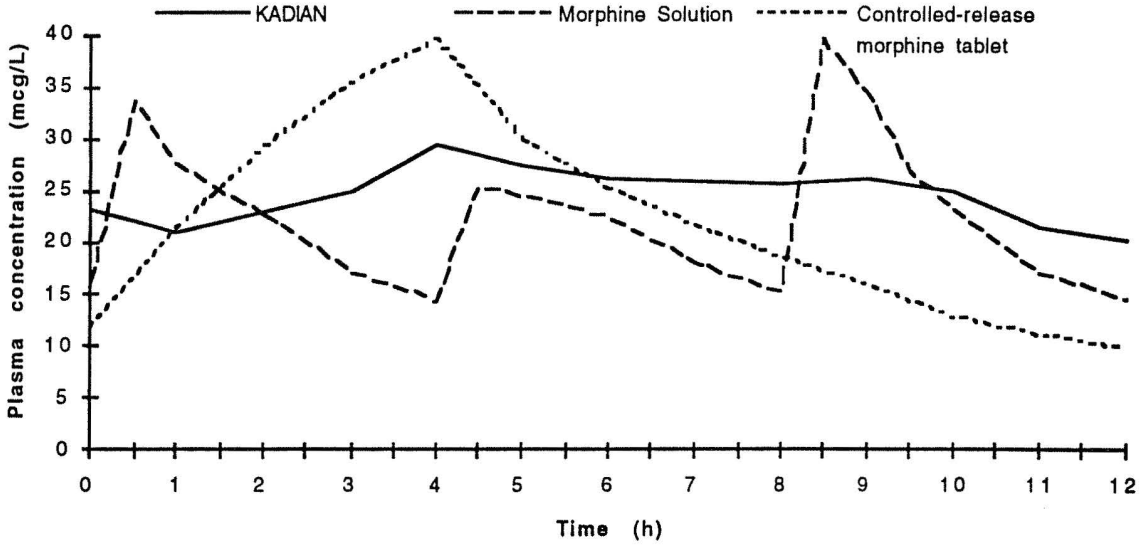
MOB1/90 (Vol. 27)

MOBES8/90, (Vol. 86) **CDD-14556,** (Vol. 60) **MOR-9/92** (Vol. 77)

For any fixed dose and dosing interval, KADIAN will have at steady state a significantly lower C_{max} and a higher C_{min} than oral morphine solution and other controlled-release preparations (see graph below), but will be therapeutically similar with regard to pain control and adverse events.

MOB1/90 (Vol. 27)

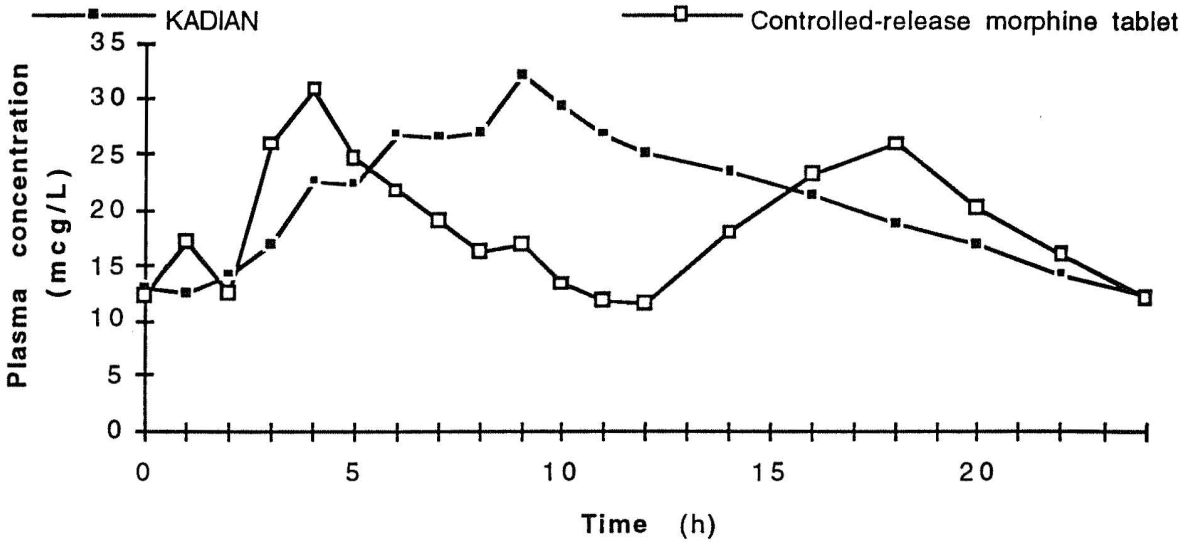
Mean steady state plasma morphine concentrations for KADIAN™ 50 mg (every 12 hours), controlled-release morphine tablet 50 mg (every 12 hours) and oral morphine solution 1 6.7 mg (every 4 hours); plasma concentrations were dose normalised.



MOR-9/92 (Vol. 77)

When given once-daily (every 24 hours) KADIAN will have at steady state a similar C_{max} and C_{min} when compared to twice-daily (every 12 hours) controlled-release morphine tablet (see graph below).

Mean steady state plasma morphine concentrations for KADIAN™ 100 mg (every 24 hours), controlled-release morphine tablet 50 mg (every 12 hours); plasma concentrations were dose normalised.



Morphine is converted to the active metabolite morphine-6-glucuronide. As accumulation of this metabolite has been demonstrated in patients with impaired renal function, caution should be exercised in patients with renal disease. While the glucuronidation pathway is intact even in cases of severe hepatic dysfunction, as with any drug, caution should be taken to adjust the dose to guard against unanticipated accumulation if renal and/or hepatic function is known to be seriously impaired.

Clinical Studies

ISS (Vol. 101)

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ISE (Vol. 100)

A total of 177 healthy subjects and 337 patients with cancer pain participated in a total of 17 studies (11 pharmacokinetic and 6 clinical). Of these individuals, 158 healthy subjects and 268 patients received KADIAN. In the controlled clinical studies patients were followed for a median duration of 7±1 days and in the uncontrolled clinical studies patients were followed for a median duration of 103 days and up to 24 months. KADIAN was compared to oral morphine solution, MST Continus®, and MS Contin® using trial designs that followed the clinical and pharmacokinetic performance of each treatment in cancer patients receiving chronic opioid therapy.

CDD-14556, (Vol. 60) **MOR-9/92** (Vol. 77)

ISE (Vol. 100)

At the time of submission 110 patients had received KADIAN administered once-a-day (every 24 hours). In two controlled trials patients were titrated to a stable 24-hour morphine requirement, KADIAN administered every 24 hours to 78 evaluable patients provided similar analgesia to the same amount of morphine given as MS Contin® every 12 hours.

Individualization of Dosage

The best use of opioid analgesics in the management of chronic malignant and non-malignant pain is challenging, and is well described in materials published by the World Health Organization and the Agency for Health Care Policy and Research which are available from the manufacturer upon request. KADIAN is a third step drug which is most useful when the patient requires a constant level of opioid analgesia as a "floor" or "platform" from which to manage breakthrough pain. When a patient has reached the point where comfort cannot be provided with a combination of non-narcotic medications (NSAIDs & acetaminophen) and intermittent use of moderate or strong opioids, the patient's total opioid therapy should be converted into a 24 hour oral morphine equivalent.

CDD-14556 (Vol. 60), **CDD-14922** (Vol. 76)
MOBES8/90 (Vol. 86), **MOR-5/92** (Vol. 92)

KADIAN should be started by administering one-half of the total daily oral morphine dose as KADIAN capsules every 12 hours (twice-a-day) **or** by administering the total daily oral morphine dose as KADIAN capsules every 24 hours (once-a-day). The dose should be titrated no more frequently than every-other-day to allow the patients to stabilise before escalating the dose. If breakthrough pain occurs, the dose may be supplemented with a small dose (less than 20% of the total daily dose) of an immediate-release product. Patients who are excessively sedated after a once-a-day dose or who regularly experience inadequate analgesia before the next dose should be switched to twice-a-day dosing.

CDD-14556 (Vol. 60), **CDD-14922** (Vol. 76),
MOR-5/92 (Vol. 92), **MOR-9/92** (Vol. 77)

Only the 20 mg strength should be started in patients who do not have a proven tolerance to opiates, and usually should be advanced at a rate not greater than 20 mg every-other-day. Most patients will rapidly develop some degree of tolerance, requiring dosage adjustment until they have achieved their individual best balance between baseline analgesia and opioid side effects such as confusion, sedation and constipation. No guidance can be given as to the recommended maximal dose, especially in patients with chronic pain of malignancy. In such cases the total dose of KADIAN should be advanced until the desired therapeutic endpoint is reached or clinically significant opioid-related adverse reactions intervene.

ISE (Vol. 100)

INDICATIONS AND USAGE

KADIAN is indicated for the management of pain where treatment with an opioid analgesic is indicated for more than a few days.

KADIAN was developed for use in patients with chronic pain who require repeated dosing with a potent opioid analgesic, and has been tested in patients with pain due to a variety of malignant conditions. KADIAN has not been tested as an analgesic for the treatment of acute pain or in the postoperative setting and is not recommended for such use.

CONTRAINDICATIONS

KADIAN is contraindicated in patients with a known hypersensitivity to morphine, morphine salts or any of the capsule components.

WARNINGS

(See also: CLINICAL PHARMACOLOGY)

Impaired Respiration

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs more frequently in elderly and debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction when even moderate therapeutic doses may significantly decrease pulmonary ventilation.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increases in pressure in patients with head injuries. Morphine should only be administered under such circumstances when considered essential and then with extreme care.

Hypotensive Effect

KADIAN, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a reduced blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics. (See also:PRECAUTIONS: Drug Interactions.) KADIAN may produce orthostatic hypotension in ambulatory patients.

KADIAN, like all opioid analgesics, should be administered with caution to patients in circulatory shock, as vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Gastrointestinal Obstruction

KADIAN should not be given to patients with gastrointestinal obstruction particularly paralytic ileus as there is a risk of the product remaining in the stomach for an extended period and the subsequent release of a bolus of morphine when normal gut motility is restored. As with other solid morphine formulations diarrhea may reduce morphine absorption.

ISS (Vol. 101); **Clin. Pharm.** (Vol. 59)

PRECAUTIONS

(See also: CLINICAL PHARMACOLOGY)

General

KADIAN is intended for use in patients who require continuous treatment with a potent opioid analgesic. As with any potent opioid, it is critical to adjust the dosing regimen for KADIAN for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of the initial dose of KADIAN, attention should be given to the points under DOSAGE AND ADMINISTRATION.

Cordotomy

Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive KADIAN within 24 hours of the procedure. In addition, the post-procedure titration of analgesics for such patients should be individualized to avoid either oversedation or withdrawal syndromes.

Special risk groups

KADIAN should be administered with caution, and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; patients with Addison's disease; myxodema; hypothyroidism; prostatic hypertrophy or urethral stricture.

Caution should also be exercised in the administration of KADIAN to patients with CNS depression; toxic psychosis; acute alcoholism or delirium tremens; severe kyphoscoliosis; convulsive disorders; patients about to undergo biliary surgery and patients with acute pancreatitis secondary to biliary tract disease.

Driving and operating machinery

Morphine may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Patients must be cautioned accordingly. Patients should also be warned about the potential combined effects of morphine with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol (see: Drug Interactions).

Information for Patients
If clinically advisable, patients receiving KADIAN should be given the following instructions by the physician:

1. The dose of KADIAN should not be adjusted without consulting the physician.

2. Morphine may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g. driving, operating machinery).
Patients starting KADIAN should be advised not to engage in hazardous activities until they have established that they can maintain normal alertness.

3. Morphine should not be taken with alcohol or other CNS depressants (sleeping medication, tranquilizers) because additive effects including CNS depression may occur. A physician should be consulted if other prescription medications are currently being used or are prescribed for future use.

4. For women of childbearing potential who become or are planning to become pregnant, a physician should be consulted.

5. **The pellets in KADIAN capsules should NOT be chewed, crushed or dissolved.**

Drug Interactions

CNS Depressants: Morphine should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, phenothiazines, other tranquilizers and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. When such combined therapy is contemplated, the initial dose of one or both agents should be reduced by at least 50%.

Muscle Relaxants: Morphine may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression.

Mixed Agonist/Antagonist Opioid Analgesics: From a theoretical perspective, mixed agonist/antagonist analgesics (i.e. pentazocine, nalbuphine and butorphanol) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs can intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion and significant depression of respiration, sometimes leading to coma. Morphine should not be given to patients taking MAOIs or within 14 days of stopping such treatment.

Cimetidine: There is a report of confusion and severe respiratory depression when a hemodialysis patient was administered morphine and cimetidine.

Diuretics: Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

MOBU7/90-2 (Vol. 34)

Food: The bioavailability of KADIAN is not significantly affected by food.

Non-Clin. Pharm. & Tox. (Vol. 22)

Carcinogenicity/Mutagenicity/Impairment of Fertility

Studies of morphine sulfate in animals to evaluate the drug's carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

ISS (Vol. 101)

Pregnancy

Teratogenic effects - CATEGORY C: Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is no clearly defined risk, such experience can not exclude the possibility of infrequent or subtle damage to the human fetus.

KADIAN should be used in pregnant women only when the perceived need outweighs the known risks.

Nonteratogenic effects: Infants born to mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

ISS (Vol. 101)

Labour and Delivery

KADIAN is not recommended for use in women during and immediately prior to labor, where shorter acting analgesics are more appropriate. Infants born to mothers receiving opioid analgesics during labour should be observed closely for signs of respiratory depression. In such infants, a specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression.

ISS (Vol. 101)

Nursing Mothers

Low levels of morphine sulfate have been detected in human milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Nursing should not be undertaken while a patient is receiving KADIAN since morphine may be excreted in the milk.

Pediatric Use

KADIAN has not been evaluated in children.

ISS (Vol. 101)

ADVERSE REACTIONS

The adverse reactions caused by morphine are essentially the same as those observed with other oral and parenteral opioid analgesics. They include the following major hazards: respiratory depression, apnea and to a lesser degree; circulatory depression, respiratory arrest, shock and cardiac arrest.

More common adverse reactions that are due to the pharmacological activity of morphine are: constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria and euphoria.

Management of Excessive Sedation: Most patients receiving morphine will experience initial drowsiness. This usually disappears in three to five days and is not a cause of concern unless it is excessive, or accompanied with unsteadiness or confusion. Dizziness and unsteadiness may be associated with postural hypotension, particularly in elderly or debilitated patients.

Excessive or persistent sedation should be investigated. Factors to be considered should include: concurrent sedative medications, the presence of hepatic or renal insufficiency, hypoxia or hypercapnia due to exacerbated respiratory failure, intolerance to the dose used (especially in older patients), disease severity and the patient's general condition.

The dosage should be adjusted according to individual needs but because of reduced clearance and/or increased pharmacodynamic sensitivity, dosage may be lower in patients over 50 years of age compared to younger patients. If the dose of KADIAN is reduced and pain is not adequately controlled, the dose may be carefully increased every second day.

Management of nausea and vomiting: Nausea and vomiting is common after single doses of morphine or as an early undesirable effect of regular opioid therapy. The prescription of a suitable antiemetic should be considered. The frequency of nausea and vomiting usually decreases within a week or so but may persist due to opioid-induced gastric stasis. Metoclopramide is often useful in such patients.

Management of constipation: Virtually all patients suffer from constipation while taking opioids on a chronic basis. Some patients, particularly elderly, debilitated or bedridden patients may become impacted. Patients must be cautioned accordingly and laxatives, softeners and other appropriate treatments should be initiated from the beginning of opioid therapy.

Other Less Common Adverse Effects include:

Central Nervous System: Euphoria, dysphoria, weakness, and occasional hallucinations.

Gastrointestinal: Dry mouth, anorexia, colic, taste alterations and biliary colic.

Cardiovascular: Flushing of the face, chills, tachycardia, bradycardia, palpitations, hypotension and hypertension.

Genitourinary: Urine retention or hesitancy, reduced libido or reduced potency.

Dermatologic: Pruritus, urticaria, other skin rashes, edema and diaphoresis.

Endocrine: A syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatremia secondary to decreased free-water excretion.

Visual Disturbances: Blurred vision, nystagmus, diplopia and miosis.

Drug Abuse Liability Ass. (Vol. 103)

DRUG ABUSE AND DEPENDENCE

Morphine is the prototype of opioid agonist drugs, and may be subject to misuse, abuse and addiction. Addiction to opiates prescribed for pain management is rare, but requests for opiates from patients addicted to opioids is common and physicians should take appropriate care in prescribing this controlled substance.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with narcotic antagonist activity, e.g. naloxone or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine; See also OVERDOSAGE).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued narcotic usage. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

In chronic pain patients, and in narcotic-tolerant cancer patients, the administration of KADIAN should be guided by the degree of tolerance manifested. Physical dependence, per se, is not ordinarily a concern when one is dealing with a patient in pain, and fear of tolerance should not deter using adequate doses to adequately relieve pain.

If morphine is abruptly discontinued, a moderate to severe abstinence syndrome may occur. This is usually mild and is characterized by rhinitis, myalgia, abdominal cramping and occasional diarrhea. Most observable symptoms disappear in 5-14 days without treatment; however, there may be a phase of secondary or chronic abstinence which may last for 2-6 months characterized by insomnia, irritability and muscular aches.

If treatment of physical dependence of patients taking morphine is necessary, the patient may be detoxified by gradual reduction of the dosage. Gastrointestinal disturbances or dehydration should be treated accordingly.

OVERDOSAGE

Symptoms

Acute overdosage with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, bradycardia and hypotension.

Treatment

Primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a sustained-release formulation such as KADIAN has been taken. Care should be taken to secure the airway before attempting treatment by gastric emptying or activated charcoal.

The pure opioid antagonist, naloxone, is a specific antidote against respiratory depression which results from opioid overdose. Naloxone (usually 0.4 to 2.0 mg) should be administered intravenously; however, because its duration of action is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. KADIAN will continue to release and add to the morphine load for up to 12 hours after administration and the management of morphine overdose should be monitored accordingly. If the response to naloxone is suboptimal or not sustained, additional naloxone may be re-administered, as needed, or given by continuous infusion to maintain alertness and respiratory function.

MOBU-7/90-2 (Vol. 34),
KAP-RRC/91/01 (Vol. 41),
MOBU9/90 (Vol. 56),
MOBU-10/90 (Vol. 50),
MOR-8/92 (Vol. 53)

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Naloxone should be administered cautiously to persons who are known, or suspected to be physically dependent on KADIAN. In such cases, an abrupt or complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

Opioid Tolerant individuals: In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of a narcotic antagonist in such a person should be reserved to cases where such treatment is clearly needed. If necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with care and by titration with smaller than usual doses of the antagonist.

Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

DOSAGE AND ADMINISTRATION

KADIAN CAPSULES SHOULD BE SWALLOWED WHOLE. THE CAPSULES AND PELLETS SHOULD NOT BE CHEWED, CRUSHED OR DISSOLVED.

TAKING BROKEN, CHEWED OR CRUSHED KADIAN CAPSULES WILL LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

ISE (Vol. 100), **MOBES8/90** (Vol. 86), **CDD-14556** (Vol. 60), **MOB1/90** (Vol. 27), **MOR-9/92** (Vol. 77)

The sustained-release nature of KADIAN allows it to be administered on a convenient once-a-day or twice-a-day schedule . KADIAN produces analgesia similar to conventional immediate-release and other controlled-release formulations with regard to pain control for the same total daily dose of morphine. However, peak and trough blood levels depend on the release characteristics of each specific formulation, and other oral morphines may not be therapeutically equivalent to KADIAN.

ISE (Vol. 100),**CDD-14556** (Vol.60), **MOR-9/92** (Vol.77), **MOBES8/90** (Vol. 86)

HPB Sum. (Vol. 26)

KAP-RRC/91/01 (Vol. 41), **MOB1/90** (Vol. 27), **MOR-9/92** (Vol. 77) **ISE** (Vol. 100); **Clin. Pharm.** (Vol. 59)

KADIAN capsules have the same extent of absorption (AUC) as immediate-release oral formulations and controlled-release oral formulations of morphine sulfate. However, key pharmacokinetic parameters (e.g., C_{max}, T_{max}) for KADIAN are significantly different to other controlled-release oral formulations so that they are not strictly bioequivalent to KADIAN.

MOB1/90 (Vol. 27), **KAP-RRC/91/01** (Vol. 41), **MOBU7/90-2** (Vol. 34) **HPB Sum.** (Vol. 26)

As with any potent opioid drug product, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of KADIAN, attention should be given to:

1) the total daily dose, potency and kind of opioid the patient has been taking previously;
2) the reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed;
3) the patient's degree of opioid tolerance;
4) the general condition and medical status of the patient;
5) concurrent medication;
6) the type and severity of the patient's pain.

The following dosing recommendations, therefore, can only be considered suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of an individual patient.

Conversion from Other Oral Morphine Formulations to KADIAN

CDD-14556 (Vol. 60), **CDD-14922** (Vol. 76), **MOBES8/90** (Vol. 86), **MOR-5/92** (Vol. 92) **ISE** (Vol. 100)

Patients on other oral morphine formulations may be converted to KADIAN by administering one-half of the patient's total daily oral morphine dose as KADIAN capsules every 12 hours (twice-a-day) **or** by administering the total daily oral morphine dose as KADIAN capsules every 24 hours (once-a-day). The dosing interval of KADIAN should not be reduced below every 12 hours.

ISE (Vol. 100), **CDD-14556**(Vol. 60), **CDD-14922** (Vol. 76), **MOR-5/92** (Vol. 92), **MOR-9/92** (Vol. 77)

Conversion from Parenteral Morphine or Other Parenteral or Oral Opioids to KADIAN

KADIAN can be administered as the initial oral morphine drug product. While there are useful tables of oral and parenteral equivalents in cancer analgesia, there is substantial interpatient variation in the relative potency of different opioid drugs and formulations. For these reasons, it is better to underestimate the patient's 24 hour oral morphine requirement and to have to increase the dose, than to overestimate and have to manage an adverse event. The following general points should be considered:

Parenteral to oral morphine ratio: Estimates of the oral to parenteral potency of morphine vary from 1:6 to 1:2 in chronic use. A dose of oral morphine three times the daily parenteral morphine requirement may be sufficient in chronic use settings.

Other parenteral or oral opioids to oral morphine sulfate: Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate (see Table 1 for oral opioid potency). In general, it is safest to give only half of the estimated daily morphine demand as the initial dose, and to deal with inadequate analgesia by supplementation with immediate-release morphine. (See discussion which follows.)

CDD-14556 (Vol. 60),
CDD-14922 (Vol. 76),
MOR-5/92 (Vol. 92), **MOR-9/92** (Vol. 77)
ISE (Vol. 100)

The first dose of KADIAN may be taken with the last dose of any immediate-release (short-acting) opioid medication due to the long T_{max} after administration of KADIAN.

Table 1: Approximate oral opioid potency ratios relative to oral morphine*

24 Hour Oral Dosage of Prior Opioid Dose		24 Hour Oral Morphine
Methadone**	1.0 mg	1.5 mg
Papaveratum	1.0 mg	1.5 mg
Oxycodone	1.0 mg	1.0 mg
Morphine solution	1.0 mg	1.0 mg
MS Contin®	1.0 mg	1.0 mg
Roxanol™	1.0 mg	1.0 mg

* Adapted from Twycross and Lack, (1989). Oral morphine in advanced cancer. 2nd ed. Beaconsfield

** Methadone has a prolonged and highly variable plasma half-life, which leads to cumulation when given repeatedly. This estimate is only an approximation for the first dose.

Use of KADIAN as the First Opioid Analgesic

There has been no evaluation of KADIAN as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient to adequate analgesia using a sustained-release morphine, it is ordinarily advisable to begin treatment using an immediate-release morphine formulation.

CDD-15220, CDD-14785, MOR-7/92, MOR-10/92

ISE (Vol. 100)
CDD-14556 (Vol. 60), **MOR-9/92** (Vol. 77)

HPB Sum. (Vol. 26),
MOBU7/90-2 (Vol. 34),
KAP-RRC/91/01 (Vol. 41)

Considerations in the Adjustment of Dosing Regimens

Whatever the approach, if signs of excessive opioid effects are observed early in the dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, 'breakthrough' pain occurs when KADIAN is administered on an every 24 hours dosing regimen, consideration should be given to dosing every 12 hours. If breakthrough pain occurs on an every 12 hours dosing regimen a supplemental dose of a short-acting analgesic may be given. As experience is gained, adjustments in both dose and dosing interval can be made to obtain an appropriate balance between pain relief and opioid side effects. To avoid accumulation the dosing interval of KADIAN should not be reduced below every 12 hours.

Conversion from KADIAN to other controlled-release oral morphine formulations

HPB Sum. (Vol. 26),
KAP-RRC/91/01 (Vol. 47),
MOB1/90 (Vol. 27)

KADIAN is not bioequivalent to other controlled-release morphine preparations. Although for a given dose the same total amount of morphine is available from KADIAN as from morphine solution or controlled-release morphine tablets, the slower release of morphine from KADIAN results in reduced maximum and increased minimum plasma morphine concentrations than with other products. Conversion from KADIAN to the same total daily dose of other controlled-release morphine preparations may lead to either excessive sedation at peak or inadequate analgesia at trough and close observation is recommended.

HPB Sum. (Vol. 26), **MOB1/90** (Vol. 27)

Conversion from KADIAN to parenteral opioids

When converting a patient from KADIAN to parenteral opioids, it is again best to select an initial dose of parenteral opioid that is about half the calculated value. For example, to estimate the required 24 hour dose of morphine for IM use, one would take the 24 hour oral morphine dose, divide by an oral to parenteral conversion ratio of 6:1, divide the estimated 24 hour parenteral demand by the number of doses (6 for a 4 hourly dosing regimen), then halve this dose as an initial trial.

For example, to estimate the required 24 hour dose of morphine for IM administration, use a conversion of 1 mg of morphine IM for every 6 mg of morphine as KADIAN. The IM 24 hour dose is then divided by 6 and administered 4 hourly.

This approach is likely to require a dosage increase in the first 24 hours for many patients, but is recommended because it is less likely to cause overdose than trying to establish an equivalent dose without titration.

Opioid analgesic agents may not effectively relieve dysesthetic pain, post-herpetic neuralgia, stabbing pains, activity-related pain, and some forms of headache. This does not mean that patients suffering from these types of pain should not be given an adequate trial of opioid analgesics. However, such patients may need to be promptly evaluated for other types of pain therapy.

Safety and Handling

KADIAN consists of closed hard gelatin capsules containing polymer coated morphine sulfate pellets that pose no known handling risk to health care workers. Oral morphine products are not known to be associated with a high risk of diversion, but all strong narcotics are liable to diversion and misuse both by the general public and health care workers, and should be handled accordingly.

HOW SUPPLIED

KADIAN capsules contain white to off-white or tan colored polymer coated sustained-release pellets of morphine sulfate and are available in three dose strengths:

20 mg size 4 capsule, clear cap imprinted 'K 20' and clear body imprinted with two black bands.

50 mg size 2 capsule, clear cap imprinted 'K 50' and clear body imprinted with three black bands.

100 mg size 0 capsule, clear cap imprinted 'K 100' and clear body imprinted with four black bands.'

Store capsules at controlled room temperature 15° to 30°C (59°-86°F). Protect from light and moisture.

Dispense in sealed, tamper-evident, childproof, light-resistant container.

CAUTION

DEA Order Form Required.

Federal law prohibits dispensing without prescription.

Revision date: June 22, 1995

000108

APPLICATION SUMMARY

2. PHARMACOLOGIC CLASS, SCIENTIFIC RATIONALE, INTENDED USE AND POTENTIAL CLINICAL BENEFITS

KADIAN™ is an sustained-release oral formulation of morphine sulfate, an opioid analgesic derived from the milky juice of the opium poppy *(Papaver somniferum)* which has been developed by F. H. Faulding & Co. Limited, an Australian pharmaceutical company.

Chemically, morphine sulfate is 7,8-didehydro-4,5 (∝)-epoxy-17-methyl-morphinan-3,6 (∝) diol sulfate (2:1) (salt) pentahydrate. It occurs as a white, odorless crystalline powder with a bitter taste. It is soluble 1 in 21 in water and 1 in 1000 in alcohol, but is practically insoluble in chloroform and ether. The octanol:water partition coefficient of morphine is 1.42 at physiologic pH and the pKb of 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4). Morphine sulfate melts at about 250°C, with decomposition.

Morphine is a natural product that is the prototype for the class of natural and synthetic opioid (narcotic) analgesics. Opioids produce a wide spectrum of pharmacologic effects including analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release and physical dependence.

Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors (μ, δ, κ) located throughout the body. Morphine acts as a pure agonist, binding with and activating the μ–opioid receptor at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

Due to extensive presystemic metabolism, the bioavailability following oral administration of morphine has been reported to be 20 - 40% but there are pronounced differences between individuals. The elimination half-life of morphine has been reported as 2 to 4 hours. Morphine is conjugated in the liver to produce morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6-glucuronide has been shown to have analgesic activity in both animal models and in man.

SCIENTIFIC RATIONALE

Following the administration of conventional immediate-release oral morphine products, approximately fifty percent of the morphine that will reach the central compartment intact reaches it within 30 minutes. This, combined with the short elimination half-life of morphine, means that immediate-release formulations must be administered every 3 to 4 hours to maintain adequate control of pain.

Oral controlled-release morphine formulations have been developed to reduce the frequency of administration of morphine and consequently to improve the quality of care for relief of pain and patient compliance. These controlled-released tablets need only be given every 8 to 12 hours. However, following the administration of equal amounts of controlled-release morphine products to healthy volunteers, approximately fifty percent of morphine that will reach the central compartment intact reaches it within one and a half hours. Therefore, controlled-release tablets do not provide a smooth, sustained delivery of morphine over the dosing interval.

The rationale on which KADIAN™ is based, is the development of a truly sustained-release product which minimizes the peak to trough ratio of the concentration of morphine in plasma by controlling the rate of drug release from polymer-coated pellets. This will provide a dosage form which may be taken every 12 or 24 hours improving patient convenience and compliance and may reduce the incidence of opioid-related adverse effects and the incidence of breakthrough pain, and thus improve the quality of care for relief of pain.

KADIAN™ is designed for once or twice daily dosing. It consists of a core acting as a drug reservoir surrounded by a dissolution rate controlling polymer membrane. The coated cores (pellets) are encapsulated into hard gelatin capsules in three dosage strengths: 20 mg, 50 mg and 100 mg. The same core and pellet formulation is used for all dosage strengths with differing numbers of pellets being used to control the dose of morphine in each capsule.

The rate of release of morphine sulfate from the core is controlled by the polymer coating which consists of:

- an insoluble polymer component (ethyl cellulose),
- an enteric polymer component (methacrylic acid copolymer which is insoluble and relatively hydrophobic at pH 1.2),
- a water soluble component (polyethylene glycol, which is soluble and hydrophilic at pH 1.2) and,
- a water soluble plasticiser (diethyl phthalate).

At pH 1.2, which approximates normal human stomach conditions, the hydrophilic component of the coat dissolves and allows water to diffuse into the core containing morphine sulfate. The dissolved active diffuses out through the coat. The dissolution profile is essentially linear at this pH.

At pH's above 5.5, which approximates conditions in the human intestine, both the hydrophilic and enteric components of the coat dissolve. Thus, the rate of dissolution of morphine sulfate from the core is greater above pH 5.5.

Studies have shown that, for any fixed dose and dosing interval, KADIAN™ will have, at steady state, a significantly lower C_{max} and a higher C_{min} than oral morphine solution and other controlled-release preparations.

INTENDED USE

KADIAN™ is indicated for the management of pain where treatment with an opioid analgesic is indicated for more than a few days.

KADIAN™ was developed for use in patients with chronic pain who require repeated dosing with potent opioid analgesics, and has been tested in patients with pain due to a variety of malignant conditions. KADIAN™ has not been tested as an analgesic for the treatment of acute pain or in the postoperative setting and is not recommended for such use.

There has been no systematic evaluation of KADIAN™ as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient using a sustained-release morphine formulation, KADIAN™ is not usually recommended for initial use.

KADIAN™ releases morphine continuously over the course of the dosing interval. The sustained-release nature of KADIAN™ allows it to be administered on a convenient once-a-day or twice-a-day schedule for baseline analgesia. KADIAN™ produces analgesia equivalent to conventional immediate-release and most other controlled-release formulations with regard to pain control for the same total daily dose of morphine. However, peak and trough blood levels depend on the release characteristics of each specific formulation, and other oral morphines may not be therapeutically equivalent to KADIAN™.

As with any potent opioid drug product, it is critical to adjust the dosing regimen for each patient individually.

The selection of the initial dose of KADIAN™ should take into account various considerations, i.e. the total daily dose; potency and characteristics of previous opioid analgesics (e.g. pure agonists or mixed agonist/antagonist); the reliability of the relative potency estimate used to calculate the dose of morphine required (potency estimates vary with the route of administration); the degree of opioid tolerance; the patients' general medical condition; concurrent medication; and type and severity of pain. The use of opioid analgesics for the relief of chronic pain, including cancer pain, should only be part of a complete approach to pain control which should include other types of treatment or drug therapy, non-drug measures and psychosocial support. The initial dose in opioid naive patients should be KADIAN™ 20 mg every 12 hours.

If signs of excessive opioid effects are observed early in the dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, "breakthrough" pain occurs, a supplemental dose of a short acting analgesic may be given. The dosing interval of KADIAN™ should not be reduced below every 12 hours. As experience is gained, adjustments can be made to obtain an appropriate balance between pain relief and opioid-related adverse events. Due to the sustained-release properties of KADIAN™ dosage adjustments should generally be separated by 24 hours.

POTENTIAL CLINICAL BENEFITS

Strong opioid analgesics such as morphine are regarded as the mainstay of therapy for moderate to severe cancer pain and orally administered solutions of morphine are very effective for the treatment of such chronic pain. Good pain control in cancer involves "round-the-clock" dosage of effective analgesics which must be given "by the clock" and not only when the patients complain of pain. This treatment rationale presents limitations on the use of orally administered morphine sulfate which, because of its very short half-life, requires dosing every 3 to 4 hours.

The established pharmacokinetic profile of KADIAN™ has the clinical benefit of a 12 to 24 hour duration of action with an opioid-related adverse event profile comparable to that of other controlled-release morphine formulations. The administration of KADIAN™ results in a smooth morphine plasma concentration/time curve providing true sustained-release characteristics. Fluctuations in peak and trough concentrations are markedly reduced compared with morphine sulfate solution or other controlled-release morphine formulations. The incidence of breakthrough pain with KADIAN™ when given either 12 hourly or 24 hourly is similar to that of other controlled-release products given 12 hourly. Those episodes of breakthrough pain are controlled using a comparable number of doses and a comparable total dose of immediate-release morphine or other suitable analgesic.

Patients with chronic pain requiring treatment with a strong opioid such as KADIAN™ often consume a range of drugs. For example, cancer patients are often elderly with pre-existing illnesses requiring drug intervention. Also, additional medication may be required to manage some of the side-effects of opioid therapy such as constipation and nausea. In summary, patients with moderate to severe chronic pain often have complex pharmaceutical regimens which significantly increase the likelihood of medication error, non-compliance and drug interactions.

Extending analgesic administration to a once-daily basis provides far more than just convenience. Once-daily administration simplifies a patient's drug regimen and improves compliance, and it is well recognized that non-compliance represents a significant cost to the healthcare system, particularly if further hospitalization is required for pain stabilization. In the institutional setting, fewer doses save pharmacy and nursing time.

KADIAN™'s truly sustained-release pharmacokinetic profile offers patients a simple, convenient method of pain control allowing the patient to maintain independence and minimizing the need for nursing care.

APPLICATION SUMMARY

3. FOREIGN MARKETING HISTORY

Marketing applications for Kadian™ Capsules have been submitted in a number of foreign countries.

Kadian™ Capsules (under the trade name Kapanol®) have been approved for marketing in Australia, Denmark, the Netherlands, New Zealand and Sweden. Marketing has commenced only in Australia where the product was first marketed in August 1994.

The following table lists all countries where Kadian™ marketing applications have been made, approvals received and marketing commenced.

Kadian™ has not been withdrawn from marketing in any country.

Table 1
Foreign Marketing History - Kadian™ Capsules

Territory	Sponsor	Application	Date of Approval	Launch
Australia	Faulding	21-May-93	11-Jul-94	1-Aug-94
UK	Faulding	25-Aug-93		
Denmark	Glaxo	27-Aug-93	1-Feb-95	
Eire	Faulding	28-Sep-93		
Netherlands	Glaxo	29-Sep-93	26-Apr-95	
New Zealand	Glaxo	1-Oct-93	12-Sep-95	
Germany	Cascan	30-Nov-93		
Austria	Glaxo	30-Nov-93		
South Africa	Glaxo	29-Dec-93		
Belgium	Glaxo	5-Jul-94		
Sweden	Glaxo	15-Jul-94	22-May-95	
Norway	Glaxo	15-Jul-94		
Iceland	Glaxo	15-Jul-94		
Canada	Faulding	20-Oct-94		
Poland	Glaxo	Mar-95		
Portugal	Glaxo	5-Feb-95		

General Marketing of Morphine

Morphine is a natural product that was first described in 1840 and has been in common medicinal used ever since. Traditional forms of administration were as injection or oral solution with solid oral dosage forms being available worldwide for more than 100 years.

Several controlled-release morphine formulations including MS Contin®/MST Continus® (Purdue Frederick/Napp Laboratories) and Oramorph®/Roxanol® (Roxane Labs) have been marketed for several years.

To the best of the sponsor's knowledge Oramorph® is only marketed in the US, and MS Contin® is marketed in the following countries.

Table 2
MS Contin® Foreign Marketing History

Country	Marketed Since	Trademark
Argentina	1992	MST Continus
Australia	1991	MS Contin
Austria	1985	Mundidol
Belgium	1987	MS Contin
Canada	1986	MS Contin
Channel Islands	1982	MST Continus
Cyprus	1982	MST Continus
Czech. Rep.	1992	MST Continus
Denmark	1983	Contalgin
Egypt	1990	MST Continus
Finland	1986	Dolcontin
France	1987	Moscontin
Germany	1984	MST Mundipharma
Great Britain	1980	MST Continus
Greece	1986	Morficontin
Hong Kong	1987	MST Continus
Iceland	1984	Contalgin
Iraq	1986	MST Continus
Ireland	1981	MST Continus
Israel	1985	MCR 10, 30, 100
Italy	1988	MS Contin

Table 2 - MS Contin® Foreign Marketing History cont'd

Country	Marketed Since	Trademark
Jamaica	1983	MST Continus
Japan	1989	MS Contin
Jordan	1993	
Kenya	1987	MST Continus
Korea (South)	1985	MS Contin
Kuwait	1987	MST Continus
Malaysia	1991	MST Continus
Malta	1986	MST Continus
Mexico	1993	MST Continus
Netherlands	1986	MS Contin
New Zealand	1984	MST Continus
Norway	1986	Dolcontin
Philippines	1991	MST Continus
Portugal	1986	MST-1, 3, 6, 10
Saudi Arabia	1987	MST Continus
Singapore	1991	MST Continus
South Africa	1984	MST Continus
Spain	1988	MST Continus
Sweden	1988	Dolcontin
Switzerland	1982	MST Continus
Taiwan	1992	MST Continus
Thailand	1991	MST Continus
Turkey	1990	MST Continus
U.A.E.	1987	MST Continus
U.S.A.	1984	MS Contin
Yugosl. (Former)	1990	MST Continus

APPLICATION SUMMARY

4. CHEMISTRY, MANUFACTURING, AND CONTROL SUMMARY

A. Introduction

NDA Volume 2

KADIAN™ Morphine Sulfate Sustained-release Capsules 20 mg, 50 mg, and 100 mg have been developed by F. H. Faulding & Co. Limited, an Australian pharmaceutical company, based in Salisbury in South Australia. (Faulding Inc., the sponsor of this NDA, is a US based wholly owned subsidiary of Faulding.)

The technology applied to KADIAN™ is similar to that applied by Faulding in the development and manufacture of its other modified release products approved in the US, including Eryc® (erythromycin - enteric), Doryx® (doxycycline - delayed-release) and Austyn® (theophylline - sustained-release).

In summary, the modified release technologies developed by Faulding encompass production of a drug-containing CORE, utilizing, for example, extrusion and marumerisation or powder-layering or slurry rotorcoating drug onto a sugar sphere seed core. The modified-release characteristics are provided by spray-coating the CORE in a fluid bed with an appropriate combination of polymers to produce the PELLET. The appropriate polymers are selected to provide the combination which, when applied to the CORE, produces the required drug release profile *in vitro* and *in vivo*. Polymers are generally selected from groups which are generally recognized as safe and in use in other pharmaceutical products, are of an appropriate grade or standard and have the required properties of hydrophobicity, hydrophilicity or varying solubilities at different pH's. Drug release characteristics of a formulation are controlled by the appropriate combination of polymers and the application of the correct weight or thickness of coat.

Finally, the modified-release PELLETS may be dusted with Talc to minimize static and improve flowability, blended to produce an appropriate batch size and then encapsulated into hard gelatin capsules to produce the finished product dosage form. Generally, Faulding modified-release products rely on formulating one single PELLET or two blended PELLETS to produce all dosage strengths of a particular product. Thus the only difference between dosage strengths is the size of the capsule and quantity of PELLETS filled into that capsule.

<u>KADIAN™ Capsules</u>

KADIAN™ Capsules were developed by Faulding over the past six years. During development, the project was code-named MOLLY, and this name appears periodically throughout this NDA. Additionally, in Australia, New Zealand, Europe and Asia, KADIAN™ will be marketed under the trade name KAPANOL® and this name, which was applied to the product over several years of its development, also appears routinely throughout this NDA. Faulding certifies that MOLLY = KAPANOL® = KADIAN™ for the purposes of this NDA.

Due to DEA restrictions on the importation of finished product dosage forms containing morphine sulfate (a Schedule II narcotic), Faulding has contracted Purepac Pharmaceutical Co. of Elizabeth, New Jersey to manufacture KADIAN™ Capsules for the US market. Purepac is a majority owned and controlled subsidiary of Faulding. Purepac has designated the product "Morphine Sulfate Extended-Release Capsules".

The product will be manufactured in the so-called Modified Release suite (MRF) at Purepac which has been purpose-built to manufacture products utilizing the Faulding type of modified release technology. Faulding co-operated with Purepac in the design and construction of the suite and in the specification and design of equipment to ensure conformity between Australian and US processes and production. Packaging will occur within Purepac's packaging department (bottles) or at a contract packager for unit dose.

The Chemistry, Manufacturing, and Control section of the NDA contains all data required under 21 CFR 314.50(d)(1). Specifically it provides details on drug substance and drug product, specifications, process controls, manufacturing, container/closure systems, stability, cross-site and scale bioequivalence, clinical supplies batch records and environmental assessment.

B. Drug Substance

1. Description **NDA Volume 2**

The active drug substance, morphine sulfate, is an opioid agonist, and is considered the prototype of opiate agonist analgesics in clinical practice.

Morphine produces its therapeutic effect by interaction with one or more classes of specific opioid receptors (μ, δ, κ) located throughout the body. Morphine acts as a pure agonist, binding with and activating the μ-opioid receptor at sites in the peri-aqueductal and peri-ventricular grey matter, the ventromedial medulla and the spinal cord to produce analgesia.

Morphine is a natural product that was first described in 1840 and its chemical structure was assigned in 1925. Although it has been obtained by total synthesis, it is more easily prepared from plant materials.

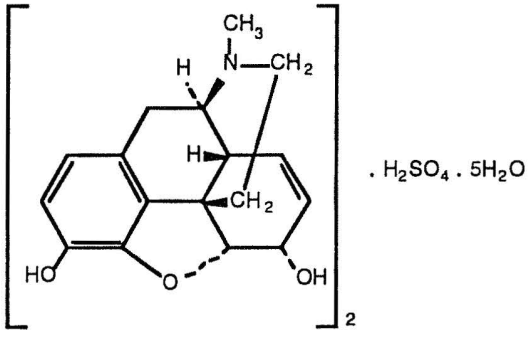
Crystalline morphine is prepared from the raw material, opium, by extraction with water, precipitation with ethanol, and purification by recrystallization as the sulfate or hydrochloride salt. The raw material, opium, containing 9-14% morphine is obtained from the milky exudate of the incised seed capsules of the poppy plant (*Papaver somniferum*) which grows in Asia Minor. Morphine is prescribed for medical use in the form of its water-soluble sulfate.

Chemically, morphine sulfate is:
7,8-didehydro-4,5∝-epoxy-17-methylmorphinan-3,6∝-diol sulfate (2:1) (salt) pentahydrate.

CAS Reg. No. is [6211-15-0].

Molecular Weight is 758.85

Structural formula is:



Morphine Sulfate is an odorless, white, crystalline powder with a bitter taste which darkens on prolonged exposure to sunlight, suggesting a light mediated transformation.

It contains not less that 98.0% and not more than 102.0% of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4$, calculated on the anhydrous basis. The known related compounds that may be encountered are normorphine, morphine-N-oxide and pseudomorphine. Codeine phosphate is also a related compound that could occur from cross contamination by the raw material manufacturer.

Chemically, morphine is classified as an alkaloid (nitrogenous base) of complex structure containing a phenolic moiety.

The melting temperature of morphine sulfate is about 250°C, with decomposition.

Morphine sulfate is very soluble in water with one gram dissolving in 15.5 mL water at 25°C, in 0.7 mL water at 80°C and relatively less soluble in organic solvents with 1 g soluble in 565 mL alcohol and insoluble in chloroform and ether. The pH of morphine sulfate solution is approximately 4.8.

Morphine sulfate does not have any known polymorphs or solvates.

The particle size of the morphine sulfate raw material is controlled by the following specifications:

- median diameter 12 μm to 25 μm
- not more than 10% greater than 50 μm
- not more than 30% less than 8.5 μm

This specification is set as part of the control of the manufacturing process and not specifically to control bioavailability. Particle size is not likely to be a significant determinant of bioavailability for a highly water soluble drug such as morphine sulfate.

2. Manufacturer of Active Ingredient **NDA Volume 2**

Faulding requests approval of the following manufacturers of Morphine Sulfate USP raw material for use in KADIAN™ Morphine Sulfate Sustained-release Capsules 20 mg, 50 mg and 100 mg:

Manufacturers:

Noramco of Delaware Inc.
500 Old Swedes Landing Road
Wilmington, Delaware 19801
(DMF Types I and II; #5775 and #6967)

and,

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017
(DMF Type II; #5857)

For more information concerning the methods of manufacture, packaging, process controls, container/closure system, stability and characteristics of the morphine sulfate, please refer to the suppliers' Type II DMF's.

C. Drug Product **NDA Volume 2**

1. Composition and Dosage Form

a. Dosage Form

KADIAN™, Morphine Sulfate Sustained-release Capsules 20 mg, 50 mg and 100 mg for oral administration have been developed by F. H. Faulding & Co. Limited at its research facilities in Salisbury, South Australia.

The drug product essentially consists of slurry coated morphine sulfate cores, polymer-coated by Wurster spray coating in a fluidized bed to form the morphine sulfate sustained-release pellets which are encapsulated into hard gelatin capsules to form the finished product dosage form. Based on assay and weight calculations, differing amounts of the same sustained-release pellets are filled into different sized capsules to produce the 20 mg, 50 mg and 100 mg dosage strengths (#4, #2 and #0 sizes, respectively).

The finished capsules are filled into bottles of 50's, 100's and 500's and into unit dose cards of 10 capsules per card, or stored in bulk in fiberboard drums.

KADIAN™ Capsules contain white to off-white or tan colored polymer coated sustained-release pellets of morphine sulfate in hard gelatin capsules (natural body/natural cap) imprinted with;

Kadian™ 20 mg: "K20" and two black bands

Kadian™ 50 mg: "K50" and three black bands

Kadian™ 100 mg: "K100" and four black bands.

Due to Drug Enforcement Administration restrictions on the importation of Schedule II narcotics, Purepac Pharmaceutical Co. of Elizabeth, New Jersey has been contracted to manufacture KADIAN™ for Faulding for the US market. Purepac Pharmaceutical Co. is a majority-owned and controlled subsidiary of Faulding. Purepac has designated the product as "Morphine Sulfate Extended-Release Capsules".

b. Components

KADIAN™ Morphine Sulfate Sustained-release Capsules, 20 mg, 50 mg and 100 mg, contain:

Core

1) Morphine Sulfate USP
2) Sugar Spheres NF, #16 to 18 mesh
3) Hydroxypropyl Methylcellulose USP, 2910, 3 cps
4) Purified Water USP
5) Alcohol USP
6) Talc USP

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Pellet

7) Ethylcellulose NF, 50 cps

8) Methacrylic Acid Copolymer NF, Type C, powder

9) Polyethylene Glycol NF, 6000

10) Diethyl Phthalate NF

11) Talc USP

12) Alcohol USP

Capsule Shell

13) #4 Gelatin NF (Natural Body/Natural Cap) (20 mg);
#2 Gelatin NF (Natural Body/Natural Cap) (50 mg);
#0 Gelatin NF (Natural Body/Natural Cap) (100 mg);
imprinted withTekPrint™ SW-9009 (black imprinting ink used to print the capsules consists of Shellac, Ethyl Alcohol, Isopropyl Alcohol, n-Butyl Alcohol, Propylene Glycol, Water, Ammonium Hydroxide, Potassium Hydroxide and Black Iron Oxide)

c. Function of Inactive Ingredients

KADIAN™ morphine sulfate sustained-release capsules comprise encapsulated polymer-coated drug pellets.

Sugar spheres, consisting of sugar and starch, constitute the seed core of the pellet. The sugar spheres provide the foundation or substrate for the core process where a morphine sulfate/binder slurry is applied to the sugar seed to produce the drug CORE. Their spherical shape and precise size distribution ensure production of spherical pellets of a well-defined size range and potency.

Hydroxypropyl methylcellulose is a low viscosity polymer that acts as a binder for the morphine sulfate onto the sugar sphere. It gives the core the ability to maintain its integrity under the conditions encountered in the spray coating procedure. Without a binder, morphine sulfate cores would be friable and would disintegrate in the subsequent manufacturing steps.

The sustained-release PELLET is manufactured by Wurster fluid bed spray coating a combination of polymers onto the drug cores. The rate of release of morphine sulfate from the pellet is controlled by the polymer coating combination which consists of ethylcellulose, methacrylic acid copolymer, polyethylene glycol and diethyl phthalate.

The ethylcellulose is a water insoluble polymer; methacrylic acid copolymer is an enteric polymer, which is insoluble and relatively hydrophobic at pH 1.2 but more soluble at pH's above 5.5; polyethylene glycol is water soluble and hydrophilic at low pH; and, diethyl phthalate is a water insoluble plasticizer, which provides flexibility and strength to the polymer coat.

The drug release characteristics of the product are determined by the combination of the polymers in the appropriate proportions and the thickness of the polymer coating applied.

At pH 1.2, simulating conditions in the human stomach, the hydrophilic component of the coat dissolves and allows fluid to diffuse into the core containing morphine sulfate. The dissolved active diffuses out through the coat. The dissolution profile is essentially linear at this pH.

At pH above 5.5, simulating conditions in the human intestine, both the hydrophilic and enteric components of the coat dissolve. Thus, the rate of dissolution of morphine sulfate from the core is greater at higher pH.

Talc is used in the pellet manufacturing process as a dry lubricant and to reduce static buildup. This allows the pellets to flow more freely during the manufacturing phase as well as the encapsulation process.

Ethanol USP and Purified Water USP are solvents in the manufacturing process and may be present in the final dosage form in trace amounts.

The polymer coated pellets are filled into imprinted hard gelatin capsules to produce the finished product dosage form.

d. Unit Dose Composition

The unit dose compositions for each dosage strength of KADIAN™ Capsules are included in the following pages.

Note: The ranges (Low: Typical: High) applied to the unit dose compositions reflect inherent variability of active ingredients in final composition due to a number of factors including slurry coating and spray coating efficiencies, allowable potency and moisture ranges and allowable sugar sphere size ranges. Final potency of morphine sulfate in finished dosage form is controlled by determination of capsule fill weight based on potency of pellets used.

d. Unit Dose Composition - KADIAN™ CAPSULES 20 mg

Component	Low (mg)	Typical (mg)	High (mg)
ACTIVE CONSTITUENT			
Morphine Sulfate USP		20.0	
OTHER CORE CONSTITUENTS			
Sugar Spheres NF, # 16-18 mesh	51.7	53.2	62.1
Hydroxypropyl Methylcellulose USP, 2910, 3 cps	1.3	1.3	1.5
Alcohol USP		*	
Purified Water USP	0.0	1.0	3.3
MODIFIED-RELEASE COATING COMPONENTS**			
Ethylcellulose NF, 50 cps	3.6	6.5	11.0
Methacrylic Acid Copolymer NF, Type C, powder	1.0	1.9	3.2
Polyethylene Glycol NF, 6000	1.3	2.3	3.9
Diethyl Phthalate NF	0.7	1.3	2.2
Talc USP	2.8	5.2	8.7
Alcohol USP		*	
DUSTING POWDER			
Talc USP	0.1	0.1	0.2
Total Fill Weight***	82.6	92.9	111.6
CAPSULE SHELL			
Gelatin NF (natural/natural)	Size 4	approx 37 mg	

* Residual levels only : Typical levels range from 300 to 1000 ppm.

** Coat weight may vary slightly as product is sprayed to a dissolution profile rather than a set thickness.

*** Total Fill Weights do not reconcile due to rounding of values previously carried out to more significant figures.

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d. Unit Dose Composition - KADIAN™ CAPSULES 50 mg

Component	Low (mg)	Typical (mg)	High (mg)
ACTIVE CONSTITUENT			
Morphine Sulfate USP		50.0	
OTHER CORE CONSTITUENTS			
Sugar Spheres NF, # 16-18 mesh	129.3	133.0	155.2
Hydroxypropyl Methylcellulose USP, 2910, 3 cps	3.3	3.3	3.9
Alcohol USP		*	
Purified Water USP	0.0	2.4	8.1
MODIFIED-RELEASE COATING COMPONENTS**			
Ethylcellulose NF, 50 cps	9.0	16.3	27.5
Methacrylic Acid Copolymer NF, Type C, powder	2.6	4.7	8.0
Polyethylene Glycol NF, 6000	3.2	5.8	9.8
Diethyl Phthalate NF	1.8	3.3	5.6
Talc USP	7.1	12.9	21.9
Alcohol USP		*	
DUSTING POWDER			
Talc USP	0.3	0.3	0.4
Total Fill Weight***	206.6	232.2	290.5
CAPSULE SHELL			
Gelatin NF (natural/natural)	Size 2	approx 62 mg	

* Residual levels only : Typical levels range from 300 to 1000 ppm.

** Coat weight may vary slightly as product is sprayed to a dissolution profile rather than a set thickness.

*** Total Fill Weights do not reconcile due to rounding of values previously carried out to more significant figures.

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d. Unit Dose Composition - KADIAN™ CAPSULES 100 mg

Component	Low (mg)	Typical (mg)	High (mg)
ACTIVE CONSTITUENT			
Morphine Sulfate USP		100.0	
OTHER CORE CONSTITUENTS			
Sugar Spheres NF, # 16-18 mesh	258.6	266.1	310.3
Hydroxypropyl Methylcellulose USP, 2910, 3 cps	6.6	6.6	7.7
Alcohol USP		*	
Purified Water USP	0.0	4.9	16.3
MODIFIED-RELEASE COATING COMPONENTS**			
Ethylcellulose NF, 50 cps	17.9	32.6	55.1
Methacrylic Acid Copolymer NF, Type C, powder	5.2	9.5	16.0
Polyethylene Glycol NF, 6000	6.4	11.7	19.7
Diethyl Phthalate NF	3.6	6.6	11.2
Talc USP	14.2	25.9	43.7
Alcohol USP		*	
DUSTING POWDER			
Talc USP	0.6	0.7	0.8
Total Fill Weight***	413.2	464.5	580.9
CAPSULE SHELL			
Gelatin NF (natural/natural)	Size 0	approx 96 mg	

* Residual levels only : Typical levels range from 300 to 1000 ppm.

** Coat weight may vary slightly as product is sprayed to a dissolution profile rather than a set thickness.

*** Total Fill Weights do not reconcile due to rounding of values previously carried out to more significant figures.

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2. Container/Closure System **NDA Volume 2**

In brief, Faulding's KADIAN™ Morphine Sulfate Sustained-release Capsules, 20 mg, 50 mg and 100 mg will be packaged in bottles, unit dose and bulk drum packages. Each commercial container, for this Schedule II drug, complies with the labeling & packaging requirements for controlled substances (21 CFR 1302).

Bottles

The bottle container/closure system will consist of a high-density polyethylene (HDPE) bottle with a plastic cap. Market packages will be available in 50, 100 and 500 capsule bottles for each of the three dosage strengths. The cap on each marketed bottle size will be available as both child-resistant or non-child-resistant. The cap for each package size will possess a liner and a tamper evident induction innerseal. Each package size will include a cotton filler.

Unit Dose

The unit dose container/closure system will consist of a polyvinyl chloride and Aclar blister film with an aluminum foil backing enclosed in a fold over paperboard card. Each unit dose package will hold 10 capsules.

Bulk

The bulk drum container/closure system will consist of two low density polyethylene liners in an 8.5 gallon, cylindrical, fiber drum, with a steel top and Lok-Rim tamper evident locking device.

These containers are used for shipment to our contract unit dose packager and for in-house storage.

3. Manufacturer **NDA Volume 3**

Faulding's KADIAN™ Morphine Sulfate Sustained-release Capsules 20 mg, 50 mg and 100 mg will be contract manufactured, packaged, labeled and tested in process, QC release and stability at the following facility:

Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, New Jersey 07207

Unit dose packaging of Faulding's KADIAN™ Morphine Sulfate Sustained-release Capsules 20 mg, 50 mg and 100 mg will be done at the following facility:

Paco Pharmaceutical Services, Inc.
1200 Paco Way
Lakewood, New Jersey 08701
DMF Type I #3347

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4. Manufacturing Process **NDA Volume 3**

KADIAN™, Morphine Sulfate Sustained-release Capsules 20 mg, 50 mg and 100 mg have been developed by F. H. Faulding & Co. Limited at its research facilities in Salisbury, South Australia.

The technology utilized by Faulding is as follows:

The core is produced by rotorgranulation in a fluid bed applying a morphine sulfate containing slurry (the GRANULATING SOLUTION/dispersion) to sugar sphere seed cores and evaporating off the solvent used to make the slurry. A binder is included to assist in adherence of the morphine sulfate to the sugar spheres and to strengthen the CORE.

A combination of three polymers (the COATING SOLUTION) is spray-coated onto the CORE in a fluid bed fitted with a Wurster spray insert. The polymers include an insoluble or hydrophobic polymer, a soluble or hydrophilic polymer and one which is insoluble at acid pH (as found in the human stomach) but soluble at higher pH (as found in the human intestine). The COATING SOLUTION also contains talc and a plasticizer for strength.

The PELLET, once the appropriate weight of polymer coat is applied, is dusted with talc to reduce static and improve flow, sieved to correct size and, if required, blended to achieve appropriate batch size.

The pellets are then filled into capsules and finally packaged in bulk, in bottles or in unit dose blisters.

At each stage and scale of manufacture a separate master formula document is prepared for each manufactured intermediate.

Attached are schematics that summarize; a) the process flow and equipment, and intermediate product stages; and b) the in-process controls and tests proposed for routine commercial operations for each intermediate.

The manufactured intermediates are not produced for a dedicated Kadian™ Capsule batch. The Q.A. released intermediates can be dispensed in portions to more than one lot of subsequent intermediate or final product.

Technology Transfer

Development scientific and engineering staff from Faulding in Australia assisted Purepac in the transfer of KADIAN™ from Australia. Based on established experience in Australia and on minor differences in operating procedures at Purepac, several minor process improvements were introduced during the transfer from Australia. Additionally, scales of production have varied across the two sites, and over the product used in early clinical trials.

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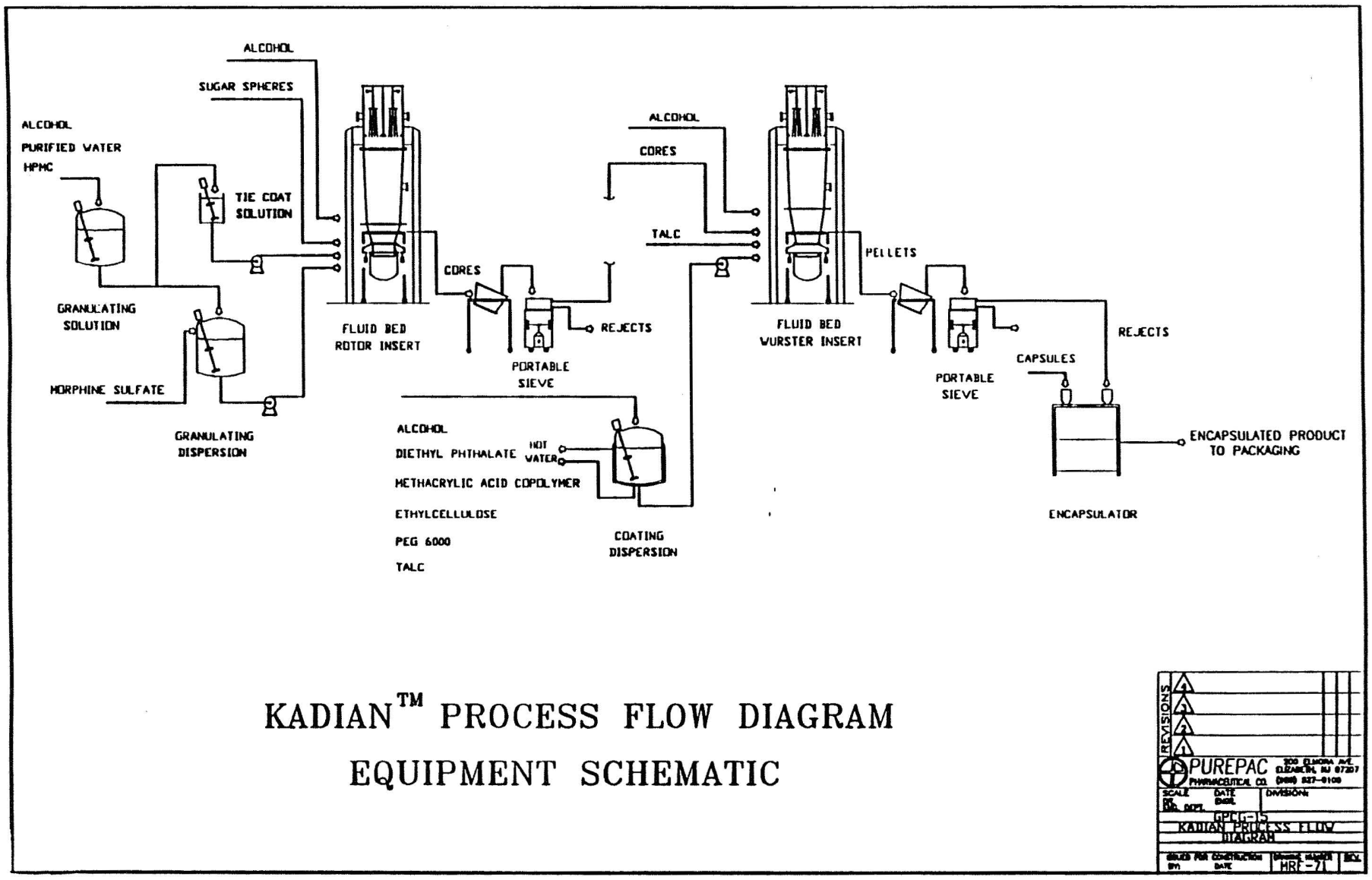
In Australia, clinical supplies have utilized both a GPCG-15 Glatt fluid bed equipped with an RG-5 rotorgranulator insert and a 9" Wurster insert; and the production scale GPCG-200 Glatt fluid bed equipped with an RG-100 rotorgranulator insert and a 32" Wurster insert. This latter unit is also used for commercial scale production in Australia.

At Purepac, two scales are available and will be utilized. Initial production scale, which was utilized for exhibit batch production, involves the use of a GPCG-15 equipped with an RG-5 rotorgranulator insert and an 18" Wurster insert. Large production scale will utilize a GPCG-200 equipped with an RG-100 rotorgranulator insert and up to a 46" Wurster insert. (A 32" Wurster insert may be utilized as an interim pellet scale if required in the future).

In order to assure that both sites (Faulding Australia and Purepac New Jersey) and all scales are equivalent, both *in vitro* and *in vivo* testing was undertaken. *In vitro* testing demonstrated that batches made at both sites and all scales are equivalent and meet the proposed product specification. An *in vivo* bioequivalence study, MOR-13/94, demonstrated bioequivalence between product made on the
GPCG-15's at both Faulding Australia and Purepac New Jersey and product made on the GPCG-200 at Faulding Australia.



KADIAN™ PROCESS FLOW DIAGRAM
EQUIPMENT SCHEMATIC

REVISIONS

PUREPAC PHARMACEUTICAL CO.

KADIAN PROCESS FLOW DIAGRAM

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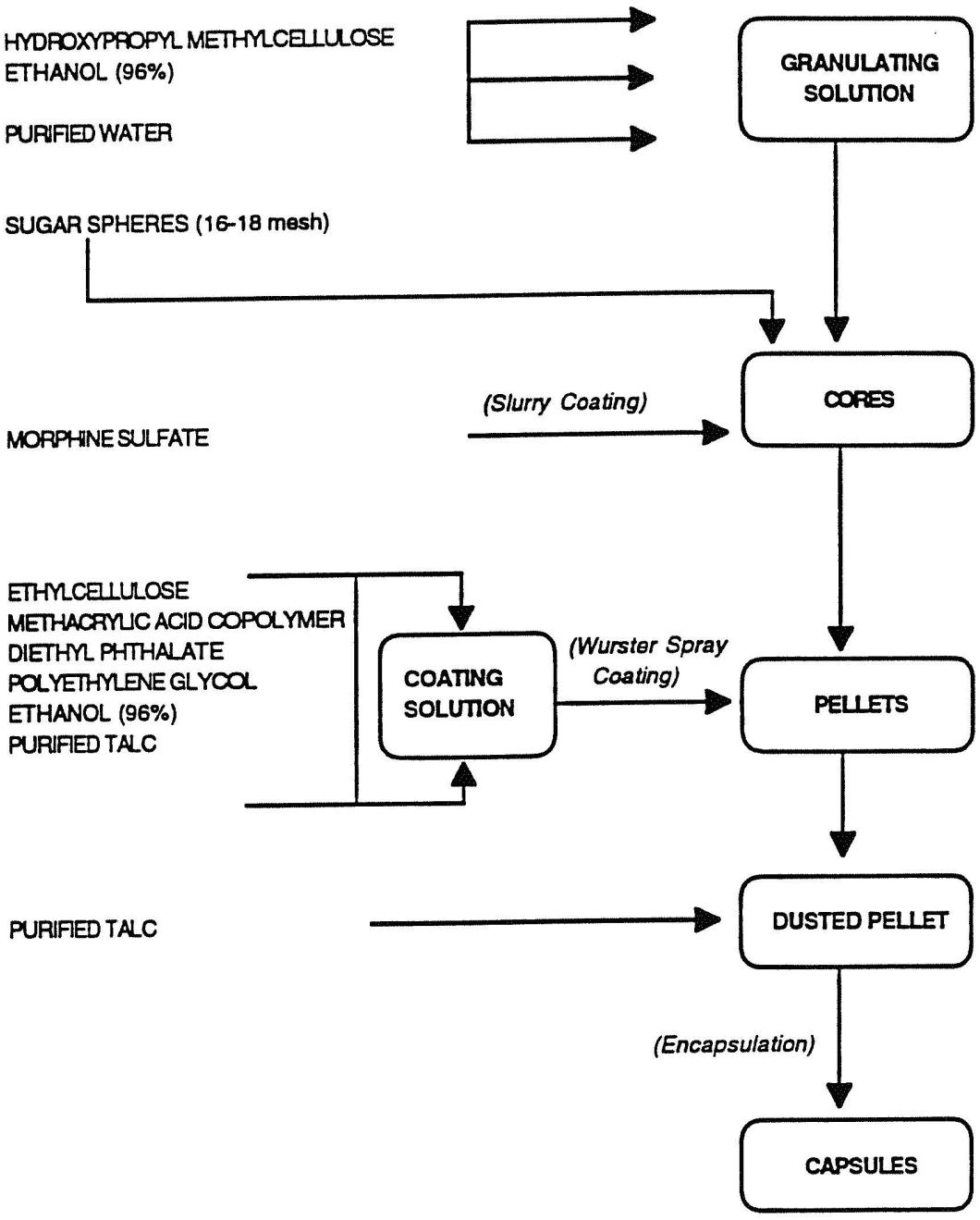
Process Flow Diagram



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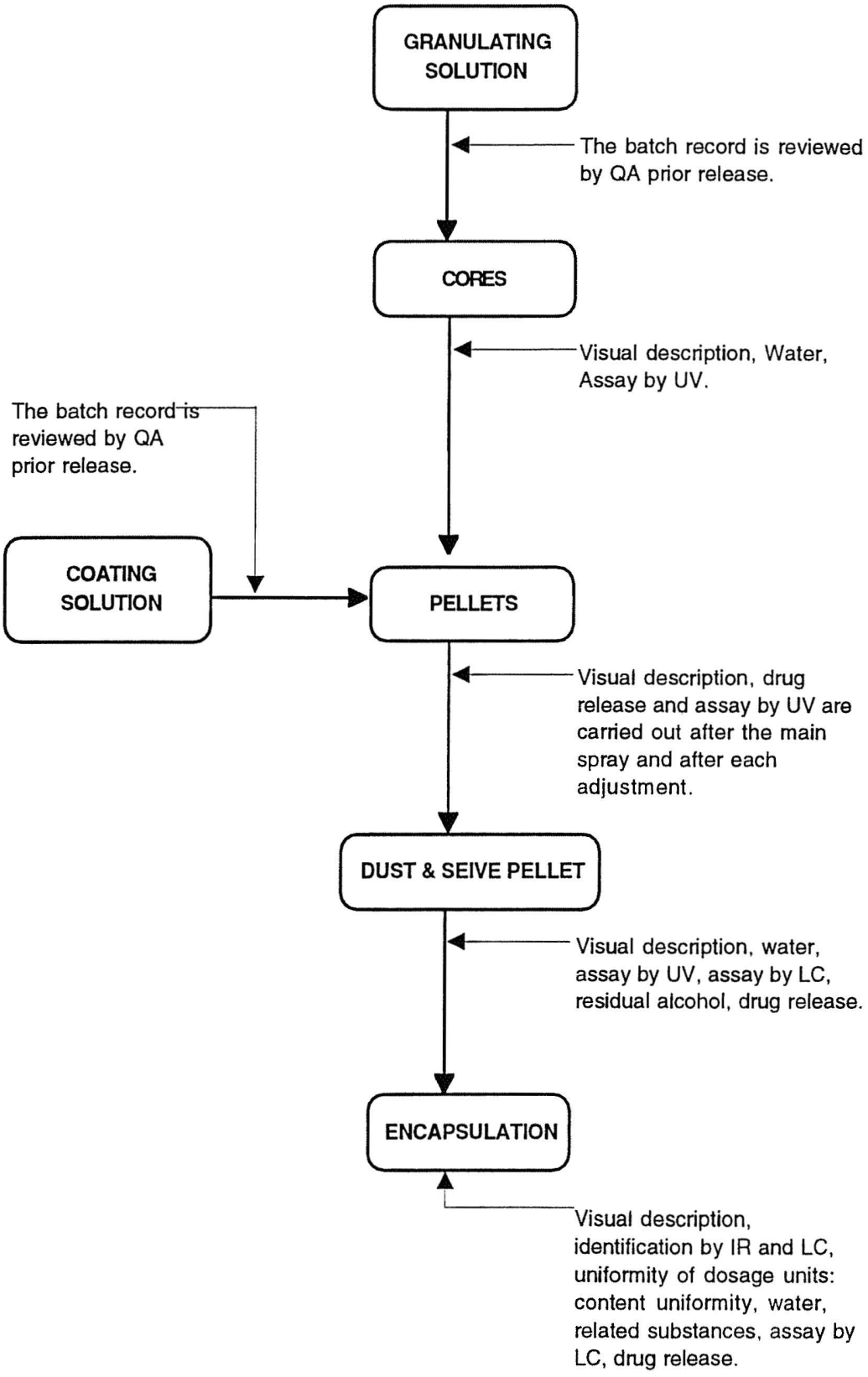
In-process Testing for Commercial Batches



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5. Stability

NDA Volume 8

Based upon satisfactory test results derived from our accelerated stability studies and upon supportive long-term data from our Australian production, Faulding will utilize an initial expiration dating period of 24 months for Kadian™ Morphine Sulfate Sustained-release Capsules, 20 mg, 50 mg and 100 mg when stored under labeled conditions of controlled room temperature 15°C to 30°C (59°F to 86°F). Expiration dating periods may be extended when satisfactory room temperature data have been accrued on three batches of the approved formulation, up to and including the test station representing the proposed dating extension.

The expiration dating for Kadian™ Capsules is based on the date of the start of manufacture (Main Spray) of the oldest pellet in the capsule batch plus the shelf life of the product.

This basis for expiration dating is taken for this sustained-release product because the rate of drug release which is controlled by the polymer coat of the pellet is the stability indicating and product performance determining parameter.

The following tables provide details of the exhibit batch and proposed commercial product stability programs.

a. Finished Product Stability

Three month accelerated and room temperature stability data are included in this application for exhibit batches covering all three dosage strengths and all pack configurations including bottles, bulk and unit dose blisters. These data are submitted in support of an initial 24 month expiration dating period for Kadian™ Capsules.

b. Intermediate Products Stability

This application provides data supporting the shelf-life and expiration dating for all Kadian™ Capsule intermediates.

Granulating Solution (14 days) and Coating Solution (30 days) were manufactured and held for their proposed shelf lives prior to use in manufacturing exhibit batches which have subsequently be placed in our exhibit bulk stability program.

This application provides for Cores and Pellets to be held for up to six months and exhibit batch Cores and Pellets have been placed on 12 months stability in support of this shelf life.

c. Supportive Data

In support of the proposed expiration date and storage conditions for intermediates and finished product, Kadian™ Capsules, stability data generated on product manufactured by Faulding in Australia, have also been included in this application. Six month stability data on four batches of Cores and Pellets are provided and stability summary data from our Australian based clinical supplies batches are also included.

Exhibit Batch Stability Program - Kadian™ Morphine Sulfate Sustained Release Capsules

Container/ Closure	Condition	Capsule Strength & Lot No.				Test Stations (months)											
		20 mg	50 mg	100 mg	50 mg	0	1	2	3	4.5	6	9	12	18	24	30	36
		PI-831	PI-830	PI-829	PI-832												
Bottles																	
50	RT	X	X	X	X	X			X		X	X	X	X	X	X	X
	ACC	X	X	X	X	X	X	X	X	X	X						
50 CRC	RT	X	X	X	X	X			X		X	X	X	X	X	X	X
	ACC	X	X	X	X	X	X	X	X	X	X						
100 CRC	RT		X			X	X	X									
500	RT	X	X	X	X	X			X		X	X	X	X	X	X	X
	ACC	X	X	X	X	X	X	X	X	X	X						
500 CRC	RT	X	X	X	X	X			X		X	X	X	X	X	X	X
	ACC	X	X	X	X	X	X	X	X	X	X						
Bulk	RT	X	X	X	X	X			X	X	X	X	X				
8.5 gal	ACC	X	X	X	X	X	X	X	X								
Blisters	RT	X	X	X	X	X			X		X	X	X	X	X	X	X
10 Units	ACC	X	X	X	X	X	X	X	X	X	X						

TESTING AT EACH STATION:

- **PHYSICAL EVALUATION**
- **WATER**
- **RELATED SUBSTANCES**
- **ASSAY**
- **DRUG RELEASE**
- **DESCRIPTION**

RT= 30° C/Uncontrolled RH
ACC= 40° C/75%RH
CRC= Child Resistant Cap

Commercial Stability Program - Kadian™ Morphine Sulfate Sustained-release Capsules

Container/ Closure	Condition	Capsule Strength & Lot No. 20 mg	50 mg	100 mg	Test Stations (months) 0	1	2	3	6	9	12	18	24	30	36
Bottles															
50	RT	X	X	X	X			X	X	X	X	X	X	X	X
	ACC	X	X	X	X	X	X	X	X						
50 CRC	RT	X	X	X	X			X	X	X	X	X	X	X	X
	ACC	X	X	X	X	X	X	X	X						
500	RT	X	X	X	X			X	X	X	X	X	X	X	X
	ACC	X	X	X	X	X	X	X	X						
500 CRC	RT	X	X	X	X			X	X	X	X	X	X	X	X
	ACC	X	X	X	X	X	X	X	X						
Blisters															
10 Units	RT	X	X	X	X			X	X	X	X	X	X	X	X
	ACC	X	X	X	X	X	X	X	X						

TESTING AT EACH STATION:	
	PHYSICAL EVALUATION
	WATER
	RELATED SUBSTANCES
	ASSAY
	DRUG RELEASE
	DESCRIPTION

RT= 30° C/Uncontrolled RH
ACC= 40° C/75%RH
CRC= Child Resistant Cap

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6. Bioequivalence of US and Australian Product **NDA Volume 10**

The clinical studies offered in support of this application utilized morphine sulfate sustained-release capsules produced by Faulding at its facility in Salisbury Australia. The active drug substance, morphine sulfate, used in Australian production was sourced from Extal, (A Division of Tasmanian Alkaloids Pty. Ltd. incorporated in Tasmania, Birralee Road, Westbury, Tasmania 7303, Australia) and from Glaxo Australia Pty Ltd, (Princes Highway, Port Fairy, Victoria 3284, Australia).

United States DEA regulations require that all opioid drug products offered for sale in the U.S. utilize domestic sources of the active drug substance and that the finished dosage form be manufactured in the United States.

To comply with these regulations, commercial production of this Class II drug has been established at Purepac Pharmaceutical Co. in Elizabeth, New Jersey and utilizing morphine sulfate sourced from Mallinckrodt Chemical Co. and Noramco of Delaware Inc. All KADIAN™ capsules for commercial distribution in the United States are to be manufactured under contract by Purepac at its facility in Elizabeth, New Jersey. Purepac is a majority-owned and controlled subsidiary of Faulding.

The information in this section in conjunction with the *in vivo* bioequivalence study, MOR-13/94, support the use of our Australian based clinical supplies in the establishment of the safety and efficacy of KADIAN™.

The three batches used in the *in vitro* equivalence and *in vivo* bioequivalence studies were manufactured at two different sites. Two of the batches were manufactured by Faulding in Australia (and are called Kapanol® Capsules) and the third was manufactured by Purepac Pharmaceutical Co. in Elizabeth, New Jersey (and called KADIAN™ Capsules).

The batches were manufactured at different scales. A GPCG-15 fluid bed was used for two of the batches with different sizes of insert. The other batch was manufactured on a GPCG-200 fluid bed which is used for large scale production of KADIAN™. A different Wurster insert size was used for each pellet batch. An RG-5 rotor was used for each of the core batches manufactured on the GPCG-15 and an RG-100 rotor was used for the core batch manufactured on the GPCG-200.

This section of the Chemistry, Manufacturing, and Control Section of the application contains comparisons of:

a. related impurity profiles for active morphine sulfate from all four sources referenced and for Kapanol® or KADIAN™ manufactured from all those sources;

b *in vivo* performance of Kapanol® or KADIAN™ batches made at each site and at three scales; and

c. *in vitro* performance of those same batches.

Conclusions are drawn that all sources of active provide similar and acceptable related impurity profiles in both drug substance and drug product and that product manufactured at both sites and all three scales are bioequivalent and equivalent in *in vitro* performance.

The table below provides a summary of the three batches of Kadian™ Capsules used in the *in vitro* and *in vivo* bioequivalence comparisons.

PRODUCT INFORMATION

Name:	Kapanol® 50 mg Capsules Test	Kadian™ 50mg Capsules Test	Kapanol® 50 mg Capsules Reference
Manufacturer:	F.H.Faulding & Co. Limited. Salisbury SA, Australia	Purepac Pharmaceutical Co. Elizabeth, NJ, USA	F.H.Faulding & Co. Limited. Salisbury SA, Australia
Batch Number:	4070045	PI-830	4175002 (capsule Batch No. 4029008)
Purpose:	Validation of Australian Production	Exhibit Batch	Clinical Supply
Active Ingredient Source:	Glaxo	Noramco	Glaxo
Equipment:	GPCG-200 RG-100 Rotor 32" Wurster	GPCG-15 RG-5 Rotor 18" Wurster	GPCG-15 RG-5 Rotor 9" Wurster
Pellet Batch Size: (Kg)	145.16	70.51 + 66.55 (2 pellet batches)	11.77
Batch Size: (No. of Capsules)	104,789	192,440	4,183
Capsule Potency:	100.1%	99.4%, 99.2%	101.2%
Date of Core Manufacture:	May 1994	October 1994	December 1993
Expiration Date:	May 1996	October 1996	December 1995

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7. Clinical Supplies **NDA Volume 12**

The Kadian™ (or Kapanol®) Capsules used in all clinical studies included in this application are essentially identical to the exhibit batches described in this application. Product has been manufactured at two sites, Faulding's manufacturing facility in Australia and Purepac in Elizabeth, New Jersey, and at three different scales as described under 6. Bioequivalence of US and Australian Product above. The manufacturing process has remained unchanged and is shown in the attached Process Flow Diagram.

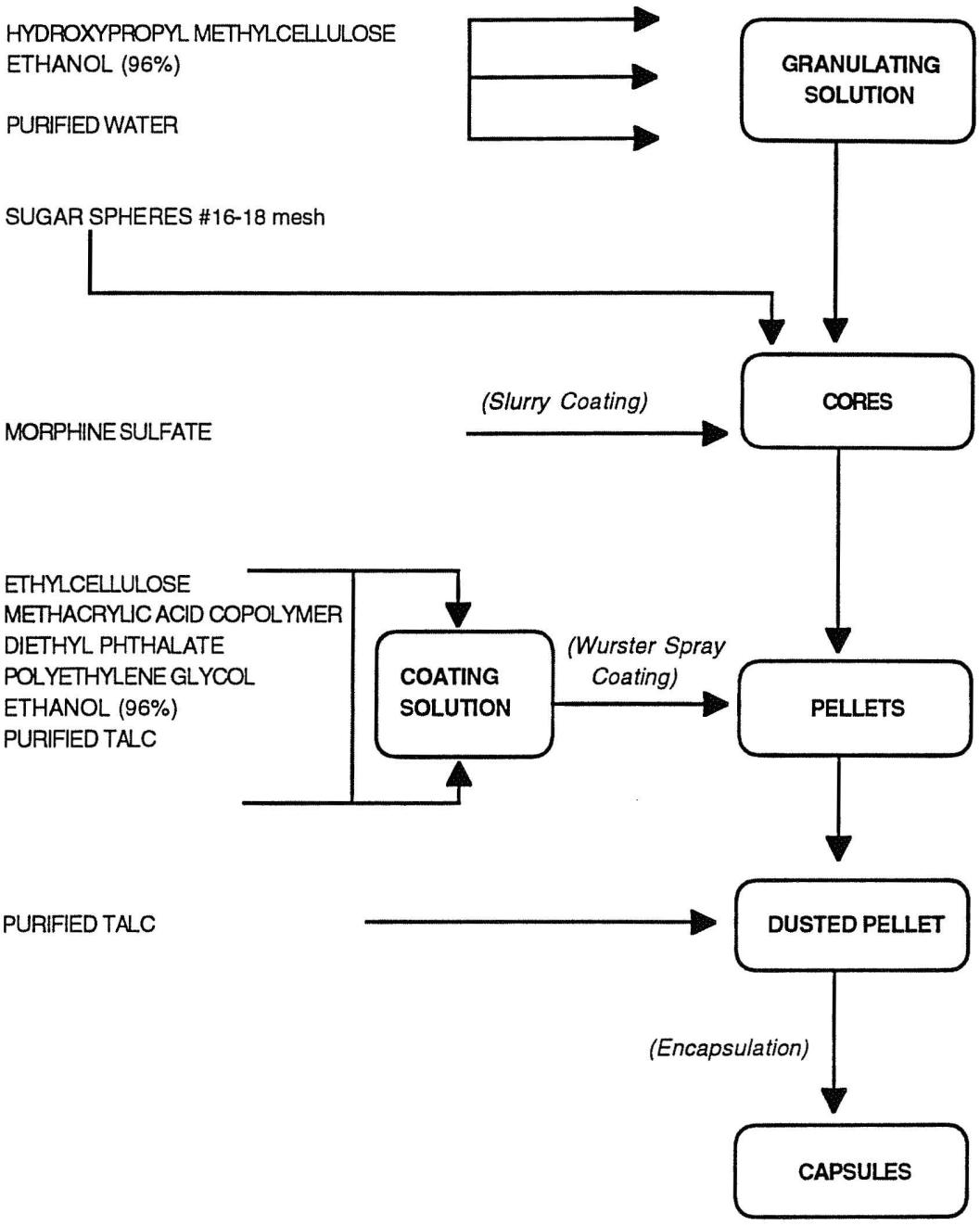
In transferring the product to the US, a minor change in potency of the CORE was made in order to ensure our capability of filling all capsule strengths using the same PELLET. The finished product capsules for all dosage strengths are all filled with the same PELLET, hence there is essentially no change in the final formulation.

Unit dose composition details are included for each dosage strength of product manufactured by Faulding in Australia and used in the clinical studies.

The Clinical Supplies Section of Chemistry, Manufacturing and Control contains information on the actives and inactives, formulation, manufacture, container-closure and stability of Kadian™/Kapanol® Capsules produced by Faulding in Australia to supply our clinical program.

The Supplies and Studies Summary Table provides a cross-reference, by study, to the source and lot number of the active drug substance, and capsule lot number and strength of Kadian™ Capsules used in each clinical study.

Clinical Supplies - Process Flow Diagram



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Clinical Supplies - Unit Dose Composition
KAPANOL® CAPSULES 20 mg

Component	Low (mg)	Typical (mg)	High (mg)
ACTIVE CONSTITUENT			
Morphine Sulfate BP		20.0	
OTHER CORE CONSTITUENTS			
Sugar Spheres NF, # 16-18 mesh	62.3	65.1	73.2
Hypromellose BP (Hydroxypropyl Methylcellulose)	1.1	1.1	1.2
Alcohol BP		*	
Purified Water BP	0.0	0.3	2.0
MODIFIED-RELEASE COATING COMPONENTS**			
Ethylcellulose NF, 50 cps	3.5	6.4	10.8
Methacrylic Acid Copolymer NF, Type C, powder	1.0	1.9	3.1
Polyethylene Glycol NF, 6000	1.3	2.3	3.9
Diethyl Phthalate BP	0.7	1.3	2.2
Purified Talc BP	3.4	6.2	10.4
Alcohol BP		*	
DUSTING POWDER			
Purified Talc BP	0.1	0.2	0.2
Total Fill Weight***	93.4	104.8	127.0
CAPSULE SHELL			
Gelatin BP (natural/natural)	Size 4	approx 38 mg	

* Residual levels only : Typical levels range from 300 to 1000 ppm.

** Coat weight may vary slightly as product is sprayed to a dissolution profile rather than a set thickness.

*** Total Fill Weights do not reconcile due to rounding of values previously carried out to more significant figures.

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Clinical Supplies - Unit Dose Composition
KAPANOL® CAPSULES 50 mg

Component	Low (mg)	Typical (mg)	High (mg)
ACTIVE CONSTITUENT			
Morphine Sulfate BP		50.0	
OTHER CORE CONSTITUENTS			
Sugar Spheres NF, # 16-18 mesh	155.6	162.8	183.1
Hypromellose BP (Hydroxypropyl Methylcellulose)	2.6	2.8	3.1
Alcohol BP		*	
Purified Water BP	0.0	0.8	5.0
MODIFIED-RELEASE COATING COMPONENTS**			
Ethylcellulose NF, 50 cps	8.9	16.1	26.9
Methacrylic Acid Copolymer NF, Type C, powder	2.6	4.7	7.8
Polyethylene Glycol NF, 6000	3.2	5.8	9.6
Diethyl Phthalate BP	1.8	3.3	5.5
Purified Talc BP	8.6	15.6	26.1
Alcohol BP		*	
DUSTING POWDER			
Purified Talc BP	0.4	0.4	0.5
Total Fill Weight***	233.7	262.3	317.6
CAPSULE SHELL			
Gelatin BP (natural/natural)	Size 2	approx 61 mg	

* Residual levels only : Typical levels range from 300 to 1000 ppm.

** Coat weight may vary slightly as product is sprayed to a dissolution profile rather than a set thickness.

*** Total Fill Weights do not reconcile due to rounding of values previously carried out to more significant figures.

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Clinical Supplies - Unit Dose Composition
KAPANOL® CAPSULES 100 mg

Component	Low (mg)	Typical (mg)	High (mg)
ACTIVE CONSTITUENT			
Morphine Sulfate BP		100.0	
OTHER CORE CONSTITUENTS			
Sugar Spheres NF, # 16-18 mesh	311.3	325.7	366.2
Hypromellose BP (Hydroxypropyl Methylcellulose)	5.3	5.5	6.2
Alcohol BP		*	
Purified Water BP	0.0	1.6	10.0
MODIFIED-RELEASE COATING COMPONENTS**			
Ethylcellulose NF, 50 cps	17.7	32.2	53.9
Methacrylic Acid Copolymer NF, Type C, powder	5.1	9.4	15.7
Polyethylene Glycol NF, 6000	6.3	11.5	19.3
Diethyl Phthalate BP	3.6	6.6	11.0
Purified Talc BP	17.1	31.2	52.1
Alcohol BP		*	
DUSTING POWDER			
Purified Talc BP	0.7	0.8	0.9
Total Fill Weight***	467.1	524.5	635.3
CAPSULE SHELL			
Gelatin BP (natural/natural)	Size 0	approx 96 mg	

* Residual levels only : Typical levels range from 300 to 1000 ppm.

** Coat weight may vary slightly as product is sprayed to a dissolution profile rather than a set thickness.

*** Total Fill Weights do not reconcile due to rounding of values previously carried out to more significant figures.

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Clinical Supplies

Supplies and Studies Summary

CAPSULE LOT NO.: STRENGTH	SOURCE BULK DRUG	MOBES-8/90	CDD-14556	CDD-14785	MOR-2/92	MOR-9/92	MOS-1/91	MOS-2/91	MOS-3/91	MOR-3/92	CDD-15220	MOR-5/92	MOR-7/92	MOR-10/92	MOBU-7/90-2	MOB-1/90	KAP-RRC-91/01	MOBU-9/90	MOBU-10/90	MOR-8/92	MOR-13/94
		CONTROLLED STUDIES					UNCONTROLLED STUDIES								BIOAVAILABILITY /PHARMACOKINETIC STUDIES						
DRUG PRODUCT																					
D4632 : 10	Extal																	√			
D3837 : 20	Extal	√							√							√		√			
D3836 : 50	Extal	√							√						√	√	√	√	√		
D3835 : 100	Extal	√							√							√		√			
D3840 : 20	Extal	√					√	√	√	√						√					
D3839 : 50	Extal	√					√	√	√	√											
D3838 : 100	Extal	√					√	√	√	√						√					
D4702 : 20	Extal		√	√	√			√	√	√	√	√	√	√							
D4701 : 50	Extal		√	√	√					√	√	√	√	√							
D4700 : 100	Extal		√	√	√		√	√	√	√	√	√	√	√							
D4593 : 50	Extal																		√		
D4594 : 50	Extal																		√		
D7089 : 50	Glaxo																			√	
D7093 : 50	Glaxo																			√	
D7134 : 50	Glaxo																			√	
D7092 : 50	Glaxo																			√	
3082001: 20	Glaxo		√	√	√	√					√	√	√	√							
3085013:100	Glaxo		√	√	√	√					√	√	√	√							
3080008: 50	Glaxo		√	√	√	√					√	√	√	√							
4029008: 50	Glaxo																				√
4070045: 50	Glaxo																				√
PI-830 : 50	Noramco																				√
DRUG SUBSTANCE																					
5689	Extal																				
QC 993D		√							√						√	√	√	√	√		
5712	Extal																				
QC 1050D		√					√	√	√	√						√					
QC 1062D																			√		
5738	Extal																				
QC 1199D			√	√	√		√	√	√	√	√	√	√	√							
MSO 0010	Glaxo																				
QC 12184			√	√	√	√					√									√	
MSO 0018	Glaxo																				
QC 22184			√	√	√	√					√										
MSO 0006	Glaxo																				
QC 62125																				√	
MSO 0044	Glaxo																				
QC 53197																					√
MSO 0048	Glaxo																				
QC 84031																					√
QC 394077																					√
94PMS012A	Noramco																				
QC 95-40101																					√

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APPLICATION SUMMARY

5. NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

NDA Volume 22

Discussions between Faulding and the FDA's Pilot Drug Evaluation Staff on February 9, 1993 indicated that for a compound such as morphine sulfate, whose pharmacodynamics and pharmacokinetics have been well established in animals and humans, a review of the published literature related to non-clinical pharmacology/toxicology studies would be considered adequate. Therefore no original preclinical data are being submitted. The report and summary submitted are based on a literature review, with the published papers reviewed being included in this application.

Kadian™ Capsules are indicated for the prolonged relief of chronic, moderate to severe pain. They are intended for patients who require repeated dosing with potent opioid analgesics over a period of more than a few days.

The rationale on which Kadian™ is based, is the minimization of the peak to trough ratio of the concentration of morphine in plasma by controlling and sustaining the rate of drug release. This may reduce the incidence of adverse effects and thus improve the quality of care for relief of pain. Kadian™ is designed to be a sustained-release product, suitable for once or twice daily dosing. It consists of a core acting as a drug reservoir surrounded by a dissolution rate controlling polymer membrane. The coated cores (pellets) are encapsulated into hard gelatin capsules in three dosage strengths; 20 mg, 50 mg and 100 mg. The same core and pellet formulation is used for all dosage strengths with differing numbers of pellets being used to control the dosage strength.

In transfering the product to the US, a minor change in potency of the core was made to ensure our capability of filling all capsule strengths using the same pellet. Variations in the unit dose composition throughout this application reflect that change.

The rate of release of morphine sulfate from the core is controlled by the polymer coating which consists of:

- an insoluble polymer component (ethyl cellulose),
- an enteric polymer component (methacrylic acid copolymer which is insoluble and relatively hydrophobic at pH 1.2),
- a water soluble component (polyethylene glycol, which is soluble and hydrophilic at pH 1.2) and,
- a water insoluble plasticiser (diethyl phthalate).

At pH 1.2, the hydrophilic component of the coat dissolves and allows water to diffuse into the core containing morphine sulfate. The dissolved active diffuses out through the coat. The dissolution profile is essentially linear at this pH.

At pH 7.5, both the hydrophilic and enteric components of the coat dissolve. Thus, the rate of dissolution of morphine sulfate from the core is greater at pH 7.5.

Typical Unit Dose Composition - Kadian™ Capsules (mg)

	20 mg	50 mg	100 mg
Core Components			
Morphine Sulfate USP	20.0	50.0	100.0
Sugar Spheres NF, #16-18 Mesh	65.1	162.8	325.7
Hydroxypropyl Methylcellulose USP, 2910, 3 cps	1.1	2.8	5.5
Purified Water USP	0.3	0.8	1.6
Alcohol USP (processing solvent - residual quantities remain in cores)			
Modified Release (Pellet) Coating Components			
Ethylcellulose NF, 50 cps	6.4	16.1	32.2
Methacrylic Acid Copolymer, NF, Type C, Powder	1.9	4.7	9.4
Polyethylene Glycol NF, 6000	2.3	5.8	11.5
Diethyl Phthalate NF	1.3	3.3	6.6
Talc USP	6.2	15.6	31.2
Alcohol USP (processing solvent - residual quantities remain in coat)			
Dusting Powder			
Talc USP	0.2	0.4	0.8
Nominal Fill Weight	104.8	262.3	524.5
Capsule Shell			
Gelatin NF (Size/Ave. Wt.)	4/38	2/61	0/96

As can be seen from the compositional listing, all raw materials are pharmaceutical grade as they conform to established pharmacopeial specifications. The concentrations in the formulation, individually or in combination, administered with standard dosage regimens, are not expected to cause concern with respect to acute or chronic toxicity.

The known related substances found in the morphine sulfate raw material available in the US and used in Kadian™ are 10-alpha hydroxymorphine, morphine-N-oxide, pseudomorphine and 6-oxo-morphine, previously known as "Unknown 1." These related substances have been isolated and adequate controls are in place to ensure that their levels are not significantly increased during manufacturing and storage.

The formulation excipients and morphine sulfate related substances are present in similar quantities in a large number of already marketed products in the U.S. and are apparently of low inherent toxicity and are present in such small amounts so as not to be clinically significant. All formulation excipients are listed in the Division of Drug Information Resources, October 1993, Inactive Ingredients Guide issued by FDA, CDER, Office of Management.

Kadian™ has undergone clinical and pharmacokinetic investigation with comparison to both traditional morphine sulfate solution and MS Contin®, the lead modified release product currently on the market. Results of our clinical trials have demonstrated that Kadian™ administered every 12 or 24 hours, has equivalent safety and analgesic efficacy to morphine sulfate solution administered every 4 hours and MS Contin® administered every 12 hours.

The following summary and full report included in this application review data from over 100 published references covering the pharmacology and toxicology of morphine in a range of animal species including rats, mice, hamsters, dogs and monkeys. Wherever possible, the report follows the format specified in the FDA guidelines.

A. Pharmacology of Morphine — NDA Volume 23

1. The Opioid Receptor

   The opioid receptor has been found to be localised in nervous tissue (Beckett & Casy, 1965; Pert & Snyder, 1973).

   A number of opioid-receptor types have been identified and classified by their pharmacological specificity and actions. Table 1 (adapted from Pasternak, 1988) provides a classification of the opioid receptor subtypes and the action of agonists on them.

Table 1. Classification of opioid receptor subtypes and actions

Subtype	Agonist	Proposed Actions
mu_1	Opiates & most opioid peptides	supraspinal analgesia prolactin release free feeding & deprivation-induced feeding acetylcholine turnover in brain c atalepsy
mu_2	Morphine sulfate	respiratory depression growth hormone release (?) dopamine turnover in the brain gastrointestinal tract transit feeding most cardiovascular effects
delta	Enkephalins	spinal analgesia dopamine turnover in the brain growth hormone release (?) feeding
kappa	Ketocyclozine & dynorphin	spinal analgesia inhibition of ADH release sedation feeding
sigma	N-allyl-normetazocine	psychotomimetic effect linked to N-methyl-D-aspartate

Morphine analgesia is considered to be mediated primarily through mu receptor activation (agonist). The affinity of morphine for mu receptors is about 10-fold higher than that for delta and kappa opioid receptors (Jaffe & Martin, 1990). Two distinct subtypes of mu receptors have now been identified, and classified as mu_1 (high affinity) and mu_2 (lower affinity) (Pasternak, 1988).

2. Receptor Affinity

Receptor binding studies presented in more detail in the Nonclinical Pharmacology/Toxicology Report are summarized in Table 2.

Table 2. Receptor binding studies conducted with morphine

Species	Receptor	Findings	Reference
Bovine caudate nucleus	opioid	Potency ratio Morphine=1 M-6-G = 0.3 M-3-G =0	Christensen & Jorgensen (1987)
Rat tissue	mu delta kappa	M-6-G potent at mu- but not delta or kappa M-3-G poor affinity at all receptors.	Pasternak et al (1987)
Rat brain membrane	opioid	M-6-G less potent than morphine in displacing opioid ligands; enhanced ligand binding at low concentrations; potent *in vivo*	Abbott & Palmour (1988)
Rat tissue	mu_2 mu_1 delta	M-6-G lower affinity than morphine. No potency difference at mu_1 or delta.	Hucks et al (1992)

While numerous receptor binding studies with opioid agonists/antagonists in animal preparations have been published, the application of these findings to the clinical situation is still in its infancy (Jaffe & Martin, 1990). Any opioid drug may interact to a varying extent with all types of opioid receptors and act as an agonist, partial agonist or antagonist. The understanding of these detailed pharmacodynamic properties of opioids in the human subject is the subject of current research.

3. Animal Pharmacology Studies

The results of preclinical morphine studies predict both the therapeutic profile and the anticipated adverse event profile of morphine in humans, with target organs in the CNS, endocrine and autonomic nervous systems. This is in agreement with the indication of analgesia sought in the labeling for Kadian™ Capsules and the adverse event profile described therein.

a. Pharmacological Profile of Morphine

The principal actions of therapeutic value of morphine are analgesia and sedation. The range of pharmacological effects, both primary and secondary, as described in animal studies are summarized as follows:

i. Central Nervous System Effects
(Way & Way, 1987; Jaffe & Martin, 1990)

Analgesia	Opioid analgesics can effectively raise the threshold for pain and the reaction of the subject to pain. Analgesia is produced in a dose-dependent manner following administration to rats (Pazos & Florez, 1984).
Euphoria	The mechanism of this action is not entirely clear. Activation of dopaminergic neurons that project to the nucleus accumbens is postulated to be a critical element in the reinforcing effects of opioids and opioid induced euphoria.
Sedation	Drowsiness and sedation are observed in some morphine treated animals. In contrast to humans, a number of animal species (cats, horses, cows and pigs) manifest excitation rather than sedation when given opioids.
Respiratory Depression	The mechanism of respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centres to increases in carbon dioxide tension and to electrical stimulation.
Cough Suppression	Morphine depresses the cough reflex by a direct effect on the cough centre in the medulla. The antitussive effect usually occurs with doses of morphine lower than those required for analgesia.
Miosis	Miosis is due to an excitatory action on the autonomic segment of the nucleus of the oculomotor nerve. Little or no tolerance develops to this effect.
Hypo-thalamus	Morphine alters the equilibrium point of the hypothalamic heat-regulatory mechanisms, such that body temperature usually falls slightly. However, chronic high doses may increase body temperature.
Endocrine Effects	Morphine acts on the hypothalamus to inhibit the release of GnRH and CRF thus decreasing the circulating concentrations of LH, FSH, ACTH and beta-endorphin. Concentrations of testosterone and cortisol in the plasma decline, thyrotropin secretion is relatively unaffected and prolactin plasma levels rise.

Emesis	Morphine can activate the brain stem chemoreceptor trigger zone to produce nausea and vomiting.
Muscular Rigidity	High doses of morphine can produce muscular rigidity; catalepsy, circling and stereotypical behaviour is seen in rats and other animals. These effects are probably related to actions on opioid receptors in the substantia nigra and striatum via both dopamine and GABA receptors.

ii. Peripheral Effects
(Way & Way, 1987; Jaffe & Martin, 1990)

Cardio-vascular System	Blood pressure is usually well maintained following morphine administration unless the cardiovascular system is stressed in which case hypotension may occur. Morphine blunts thereflex vasoconstriction caused by increased P_{CO2}.
GI Tract	Although the effects of morphine on smooth muscle of the gut are generally stimulatory, constipation is a recognized effect of morphine. The effects are mediated via an action on the CNS as well as a local action.
Biliary Tract	Morphine constricts biliary smooth muscle which may lead to biliary colic. The sphincter of Oddi may constrict resulting in reflux of biliary and pancreatic secretions and elevated amylase and lipase plasma levels.
Urinary Tract	In animal studies, reduced urine output following morphine administration seems to result from increased secretion of antidiuretic hormone as well as reduced renal perfusion.
Uterus	Morphine may prolong labor due to a reduction in uterine tone caused by peripheral and central effects of morphine.

In summary, the pharmacological profile of morphine in preclinical studies correlates closely with that reported in clinical studies in patients or healthy volunteers. In humans, the clinical effects of morphine are remarkably diverse and include analgesia, drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting, cough suppression, alterations of the endocrine and autonomic nervous systems (Jaffe & Martin, 1990).

b. Pharmacological Profile of Morphine-3-glucuronide (M-3-G) and Morphine-6-glucuronide (M-6-G)

The resurgence of interest in the conjugated metabolites of morphine in the 1980s led to several *in vivo* reports which examined the analgesic potency of M-3-G and M-6-G in comparison to morphine, in a variety of test systems.

The comparative potency of morphine, M-3-G and M-6-G is summarized in Table 3.

Table 3. Comparative potency of morphine, M-3-G and M-6-G

	Morphine	M-6-G	M-3-G
Receptor Affinity			
Christensen & Jorgensen (1987)	1.0	0.3	0
Pasternak et al (1987)	1.0	1.0	0
Animal Pharmacology Studies			
Pasternak et al (1987)	1.0	20.0	0
Abbott & Palmour (1988)			
: tail immersion test	1.0	145-200	-
: formalin test	1.0	60	-
Pelligrino et al (1989)			
: ventilatory depression effects	1.0	5-10	±
Paul et al (1989)			
: subcutaneous	1.0	2.0	-
: i.c.v.; intrathecal	1.0	90; 650	
Frances et al (1990)			
: writhing test (i.c.v.)	1.0	45.0	-
: tail flick test (i.c.v.)	1.0	61.0	
Sullivan et al (1989)			
: electrophysiological studies	1.0	13.0	0

These studies have indicated the important role which the conjugated metabolites of morphine may play in its therapeutic action. It is therefore important that new clinical pharmacodynamic/pharmacokinetic studies for morphine address the relative contribution of M-6-G, in particular, to the therapeutic effect and adverse event profile of morphine.

4. Potential Drug Interactions

A tabulated summary of the published literature related to animal studies which reported potential drug interactions likely to be of some clinical relevance are listed in Table 4. Drug interactions which have been confirmed in human subjects are included in the labeling for Kadian™ Capsules.

Table 4. Potential drug interactions reported in animal studies

Drug	Species	Interaction	Mechanism/signif.	Reference
Clonidine	rat	Synergy of spinal antinociception	Useful clinical means to maximize analgesia	Ossipov et al (1990)
Chloram-phenicol	rat	Increased morphine inhibition of self stimulatory behaviour	Alteration in protein synthesis	Copeland & Pradham (1989)
5-hydroxy tryptophan	rat	Significantly attenuated morphine response in formalin test	Contraindication for tryptophan precursors and morphine in pain management	Abbott & Young (1988)
Nomifensine	rat	x3 increase in circling induced by morphine	Blockade of dopamine receptor responsible for circling behaviour	Gratton et al (1988)
Desipramine	rat	Enhanced intensity & duration of morphine analgesia(tail flick)	Inhibition of metabolism of morphine	Goldstein et al (1982)
Methadone	rat	Morphine pretreatment prolonged methadone analgesia & increased methadone brain levels		Liu & Wang (1985)
Probenecid Sulphinpyrazone	rat	Potentiate morphine analgesia (writhing test) but no effect on duration (tail flick latency)		Morin & Lyness (1983)
Reserpine	rat	Inhibits anti-diarrhea action of morphine	Peripheral action on muscarinic receptors	Stewart (1981)
Propranolol	rat	Toxicity of morphine greatly increased	Unrelated to beta-blockade	Davis & Hatoum (1979)
Pimozide Fluoxetine	cat	Increase in hyper-thermic response to morphine	Altered balance of 5HT: dopamine receptors for thermoregulation	French et al (1978)

B. Acute Toxicity Studies

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1. LD_{50} Values

Similar values for the LD_{50} for morphine sulfate have been reported in a variety of studies and are summarized in Table 5.

Table 5. Mean LD_{50} mg/kg (95% confidence limits) of morphine sulfate in mice

LD_{50} mg/kg	n	Route	Reference
480 (428-538)	8 gravid	s.c.	Russell et al (1980)
520 (488-603)	8 non-gravid		
370 (340-441)	8	i.p.	Botting et al (1978)
470 (446-496)	5	i.p.	Davis & Brister (1971)
675 (527-864)	10	s.c.	Fennessy & Fearn (1969)
250 (211-308)	10	i.v.	Fennessy & Fearn (1969)

The mean LD_{50} values reported in the mouse ranged from 250-675 mg/kg via the s.c., i.v. or i.p. route of administration.

2. Acute Oral Toxicity Studies

The LD_{50} values reported after single oral administration of 500-1858 mg/kg morphine sulfate to the mouse and 600-1792 mg/kg morphine sulfate to the rat are summarised in Table 6.

Table 6. LD_{50} values following oral morphine sulfate in male and female mice* (Mitsuzono et al, 1987)

Species	Sex	LD_{50} (mg/kg) (95% confidence limits)
Mouse n=7	Male	1249 (1063-1493)
	Female	1125 (945-1346)
Rat n=7	Male	1025 (919-1143)
	Female	973 (849-1120)

* 7 animals were tested at each of the 6 dose levels per species

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Table 7 summarizes the histopathological findings following acute oral administration of morphine sulfate (Mitsuzono et al, 1987).

Table 7. Histopathological findings in mice and rats after single oral administration of morphine sulfate

Histopathological findings		Species (Strain)	Mouse (ICR)								Rat (Wistar)							
		Group	Dead				Survived				Dead				Survived			
		Dose (mg/kg)	1,099		1,429		1,099		1,429		864		1,037		864		1,037	
		Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
		No. of animals	2	3	3	3	3	2	3	3	1	3	3	3	3	3	3	3
	Congestion		2	3	3	3	0	0	0	0	1	3	3	3	0	0	0	0
Liver	Necrosis of centrilobular hepatocytes		0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0
	Focal necrosis of hepatocytes in subcapsular area		0	0	0	0	0	1[a)]	2	0	0	0	0	0	0	0	0	0
	Focal calcification of hepatocytes in subcapsular area		0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0
Lung	Congestion and edema		0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
Adrenal	Congestion		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0

M: Male
F: Female
a) And appearance of hemosiderin laden macrophages

In summary, the findings of the acute toxicity studies could be predicted from the known pharmacological profile of morphine and the exaggeration of its pharmacological actions in the overdose situation. Histopathological findings in mice and rats indicated that the target organs for toxicity were the liver (congestion, necrosis and calcification of hepatocytes), lung (congestion and edema) and adrenals (congestion).

C. Multidose Toxicity Studies — NDA Volume 23

In man, morphine produces a wide spectrum of unwanted effects including respiratory depression, nausea, vomiting, dizziness, mental clouding, dysphoria, pruritis, constipation, increased pressure in the biliary tract, urinary retention, a fall in body temperature and hypotension (Jaffe & Martin, 1990). The basis of the majority of these effects can be related to the preclinical pharmacological profile of morphine previously described and to the signs/symptoms of toxicity observed in the following toxicity studies.

1. Subchronic Toxicity Studies

The major findings of the subchronic toxicity studies are summarized in Table 8. The development of tolerance to the analgesic effects of morphine and physical dependence were the principal effects seen in these studies.

Table 8. Subchronic toxicity studies conducted with morphine

Dose / route Days of admin. (sex)	Results	Reference
Species		
Rat		
0,7.5,15,25,45 mg/kg/ day i.p. for 34 consec days (male)	Tolerance & dependence seen. Parallel between analgesia tolerance & some signs of physical dependence.	Mucha et al (1979)
75 mg s.c. implants for 3 days (male)	Morphine produced marked decrease in weight & secretion of prostate & seminal vesicles. Reversal on morphine w'drawal.	Cicero et al (1975)
50 mg/kg/day s.c. for 1 to 7 days (female)	Morphine altered ovarian follicular development in immature rats.	Lintern-Moore et al (1979)
50 mg/kg/day s.c. for 4 or 9 weeks (male)	Morphine decreased LH & testosterone & reduced weight of secondary sex organs. Reversal on morphine w'drawal.	James et al (1980)
10 or 20 mg/kg/day i.p. for 14 days (male)	Both doses decreased TSH but only 10 mg/kg enhanced prolactin levels. Reversal on morphine withdrawal. No tolerance to TSH effect.	Rauhala et al (1988)
Dog		
1 mg/kg weekly s.c. for 4 wks then daily for 2 weeks (sex not stated)	Tolerance to the threshold elevating effect on tooth pulp stimulation.	Kayan & Mitchell (1968)
0.125, 0.5, 1, 2 mg/kg infusion by chronic self-administration. (3 male, 2 female)	Significant negative regression of response on dose.	Jones & Prada (1981)
Cat		
1 mg/kg weekly s.c. for 4 wks then daily for 2 weeks (sex not stated)	After chronic dosing, decrease in threshold for tooth pulp stimulation.	Kayan & Mitchell (1968)

2. Chronic Toxicity Studies

An early toxicity study by Fennessy & Fearn (1969) investigated the toxicity in rats (n= 8 per group) of morphine (25 mg/kg/day) given orally, mixed with the diet, daily for 124 days. The growth rate of the rats was significantly reduced by morphine (mean % increase in weight ± S.E.) for controls = 26.1 ± 1.3%; for morphine = 5.3 ± 2.6% ($p<0.05$). The general condition of all rats remained good. No morphological or histological abnormalities were found in liver, kidneys, brain, bone marrow, spleen, heart or GI tract.

No other chronic toxicity studies have been identified from databases of published information related to morphine.

3. Development of Tolerance

Several studies in rats have demonstrated the development of acute tolerance following morphine infusion of both the antinociceptive, hypnotic and hyperthermic actions of morphine. However the pharmacokinetics of morphine were similar in both tolerant and control rats, suggesting that the development of tolerance to morphine is not related to the pharmacokinetics of morphine in serum but may be related to modification of receptor systems in the central nervous system. (Rosetti et al, 1993, Kissin et al, 1991; Bhargava et al, 1992).

Aspects of tolerance have also been studied in mice (Abdelhamid et al, 1991) and dogs (Weisbrodt et al, 1980).

A recent proposal by Rothman (1992) suggests that the brain synthesizes and secretes neuropeptides as part of a homeostatic mechanism to attenuate the effects of morphine and endogenous opioid peptides. It is suggested that administration of morphine releases anti-opioid peptides (AOP); as more morphine is given, more AOP are released producing tolerance to the effects of morphine. Cessation of morphine or administration of naloxone produces a relative excess of AOP which is in part responsible for the withdrawal syndrome. Rothman (1992) concedes that the study of anti-opioid peptides is in its infancy.

In humans, as in animals, tolerance is a normal pharmacological response to chronic morphine therapy. It appears that tolerance develops more rapidly to some effects of morphine, eg. sedation, analgesia, emesis, respiratory depression, miosis, than to others, eg. constipation. In patients with cancer pain using oral morphine, the incidence and degree of tolerance to the analgesic effects of the drug is modest. Many patients may go for several months or sometimes years with little change in their morphine dosage (Hanks, 1992). Increases in dose are usually caused by progression of the cancer and the consequent increase in pain.

4. Development of Physical Dependence

The chronic use of opioid analgesics is associated with the development of physical dependence. This is a normal pharmacological response to the continuing use of these drugs. Physical dependence is characterized by withdrawal symptoms if treatment is stopped abruptly.

Abdelhamid et al (1991) have provided evidence for the involvement of mu and delta opioid receptors in the development of acute physical dependence to morphine. Rix and Davidson (1977) reviewed the available literature and concluded that there was no evidence for implicating gamma aminobutyric acid (GABA) in the mechanisms underlying acute or chronic effects of morphine. They suggested that the hyperexcitability of the withdrawal state could be due to an imbalance of excitatory and inhibitory neurotransmitters.

A recent study by Antkiewicz-Michaluk et al (1993) reported a reduction in morphine dependence and potentiation of analgesia by chronic co-administration of nifedipine. Pretreatment with nifedipine partially restored the analgesic action of morphine in morphine tolerant rats. However, co-administration of nifedipine with morphine in a chronic experiment did not prevent the loss of morphine efficacy but prevented naloxone withdrawal syndrome. The results suggest that morphine tolerance and physical dependence may be separated by co-administration of nifedipine, and that combined chronic treatment with morphine and nifedipine may increase the efficacy of morphine during chronic treatment and prevent development of abstinence.

While morphine has the potential for physical dependence in humans, this is not a prime concern in the management of terminally ill patients or any patients in severe pain. In patients whose pain has been relieved by other treatments dose reduction and discontinuation of morphine are possible over a few days or weeks and no special measures are required (Hanks, 1992). The proposed labeling for Kadian™ contains appropriate advice in the section headed DRUG ABUSE AND DEPENDENCE.

5. Withdrawal Syndrome

The injection of nalorphine-like antagonists to rhesus monkeys physically dependent on morphine is followed within a few minutes by a dramatic series of gross behavioural and physiologic disturbances closely resembling the disturbances occurring after withdrawal of morphine. This syndrome of precipitated abstinence has been extensively used as a pharmacologic endpoint to characterize narcotic antagonists and the relevant literature has been reviewed by Villarreal and Karbowski (1974).

In order to relate plasma morphine concentrations to the severity of abrupt withdrawal, Domino et al (1987) studied 4 chronically dependent female monkeys. Severity of withdrawal showed a negative correlation with the falling phase of plasma morphine. Under the conditions of this experiment, significant morphine withdrawal symptoms arose despite measurable plasma concentrations of morphine. The authors suggest a quantitative relationship between plasma concentrations and withdrawal for a given chronic morphine dose (3.0 mg every 6 hours) and provide a linear pharmacokinetic model to estimate the onset of symptoms following abrupt withdrawal.

Ahtee et al (1989) found that in withdrawal, noradrenaline turnover increased, dopamine and 5-HT decreased. Acute morphine accelerated the turnover of the 3 monoamines. The results suggest there are fundamental differences among the three monoaminergic systems in their ability to adapt to chronic morphine dosage.

Shaham (1993) investigated the effect of stress on oral self-administration of morphine (0.5 mg/mL) and withdrawal in rats exposed for 50 days to 15 minutes per day immobilization stress. The paired stress animals had higher levels of morphine self-administration and manifested a more severe withdrawal syndrome than those tested without stress. The role of conditioning factors was also assessed and results indicated that the learned association between exposure to stress and the drug availability may mediate in part, the stress induced enhancement of opioid self-administration and withdrawal effects.

The abrupt discontinuation of morphine in humans can result in a withdrawal syndrome similar to that described in animals. In patients with cancer pain morphine is administered on a regular basis for analgesia. This regular administration prevents the induction of the withdrawal syndrome. The proposed labeling for Kadian™ contains appropriate advice on the withdrawal syndrome in the section headed DRUG ABUSE AND DEPENDENCE.

6. Carcinogenicity Studies

A search of the published preclinical literature for morphine has revealed no carcinogenicity studies conducted with morphine sulfate. The literature search revealed one study by Friesen et al (1985) which involved carcinogenicity testing of the pyrosylates of morphine. These pyrosylates were produced in the laboratory and are not considered relevant to the clinical use of morphine.

The labeling for Kadian™ Capsules acknowledges that studies of morphine sulfate in animals to evaluate the drug's carcinogenic effect potential have not been conducted.

D. Special Toxicity Studies — NDA Volume 23

No special toxicity studies were identified in the preclinical database for morphine.

E. Reproduction Studies — NDA Volume 23

The labeling for Kadian™ Capsules indicates that adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. The Nonclinical Pharmacology/Toxicology Report reviewed the following studies from the published literature. As there is no evidence that these studies were conducted according to GLP standard, their findings can be taken as a guide only.

1. Teratology Studies

   a. Mouse

   Morphine has no teratogenic effects in mice at a s.c. dose of either 100 or 200 mg/kg/day. High morphine doses of 300-500 mg/kg/day showed decreased fetal weight, axial skeletal fusions, exencephaly and increase in partial fetal resorptions (Harpel & Gautieri, 1968). Administration of low constant s.c. doses of morphine via a miniature infusion pump from day 7 to 10 produced similar teratogenic effects to large s.c. doses described above (Ciociola & Gautieri, 1983). The dose infused was not specified in the published article.

   The teratogenic doses (>300 mg/kg/day) in mice greatly exceed the usual effective analgesic dose (10 mg/kg) in mice. Investigations of the cause of these teratogenic effects eliminated the ability of morphine to release histamine (Iuliucci & Gautieri, 1971) but implicated the ability of morphine to reduce oxygen concentration and cause hyperglycaemia in pregnant mice (Arcuri & Gautieri, 1973).

   At high doses (>300 mg/kg/day) in mice, morphine has a teratogenic effect on soft, brain and skeletal tissue. The no-effect dose in the mouse is between 200 and 300 mg/kg/day.

   b. Rat

   In pregnant rats morphine has been shown to readily cross the placenta and achieve high levels in fetuses (Gabrielsson & Paalzow, 1983). This has been shown to lead to growth retardation (35 mg/kg/day s.c.) (Fujinaga & Mazze, 1988), soft tissue anomalies (20 mg/kg/day s.c.) (Johannesson & Becker, 1972), decreased litter size, increased stillborns and increased infant mortality (40 mg/kg bd i.p.) (Zagon & McLoughlin, 1977) and depression followed by *in utero* tolerance (20 mg/kg/day i.v.) (Kirby & Holtzman, 1982).

It can be concluded that doses of morphine 25 to 40 mg/kg/day given to pregnant rats have weak teratogenic effects.

c. Hamster

In pregnant hamsters single s.c. doses of morphine have a teratogenic effect on brain and skeletal tissue over the dose range 35 to 322 mg/kg/day (Geber & Schramm, 1975).

d. Rabbits

Morphine given to pregnant rabbits at 10 to 40 mg/kg/day s.c. from Day 6 to 14 was associated with significantly increased rate of spontaneous abortion but no effect was observed on fetal lung maturity (Roloff et al, 1975). Pregnant rabbits given morphine 50 to 100 mg/kg/day s.c. prior to mating and during gestation produced fetuses with significant reductions in weight, length and weight of organs, including the brain (Raye et al, 1977).

In summary, pregnant rabbits given daily doses of morphine 10 to 100 mg/kg/day s.c. have increased rates of spontaneous abortion and decreased fetal weight and length but no teratogenic effects.

e. Sheep

Sheep fetuses infused with a constant rate of morphine of 0.075 to 80 mg/h for 2 to 6 hours, exhibited a significant abstinence syndrome (Szeto & Umans, 1985). The fetus may undergo a cycle of acute physical dependence and withdrawal following the administration of morphine.

A summary of the available teratology studies for morphine is presented in Table 9.

f. Conclusion

Reproduction studies in mice, rats and hamster show morphine has teratogenic effects on brain, soft tissue and skeletal tissue. In rabbits no teratogenic effects were observed but fetal growth was retarded. Administration of morphine to pregnant sheep for 2 hours induces an abstinence syndrome in the fetuses whilst still *in utero*. One reproduction study in mice showed no teratogenic effects at morphine 100 or 200 mg/kg/day s.c. but morphine 300 to 500 mg/kg/day s.c. had teratogenic effects. The results of these studies have been considered in the Pregnancy - Category C labeling proposed for Kadian™. This is consistent with currently approved morphine products.

Table 9. Teratology studies conducted with morphine

Species	Dose / route Days of admin.	Results	Reference
Mouse	100-500 mg/kg i.v. Days 8/9 of pregnancy	Fetal wgt reduction exencephaly, axial skeletal fusion, increase in partial fetal resorptions.	Harpel & Gautieri (1968)
	dose not stated infusion; Day 7-10 of pregnancy	Fetal wgt reduction, skeletal & soft tissue abnormalities.	Ciociola & Gautieri (1983)
Rat	20 mg/kg s.c. Days 2-5,7-9,11-13	No signif wgt changes. No gross anomalies, hydronephrosis (1).	Johannesson & Becker (1972)
	10-40 mg/kg i.p. bd 5 days pre-mating & during pregnancy/ lactation	Decreased litter sizes Maternal weight loss. increased no. stillborns, infant mortality; retardation of body growth in morphine offspring.	Zagon & McLoughlin (1977)
	20 mg/kg/day i.v. Day 12 to end of gestation	Fetus showed morphine induced depression of spontaneous activity & later developed tolerance to depressant effect *in utero*.	Kirby & Holtzman (1982)
	2.5 mg/kg i.v. bolus or 23.3 µg/min/kg (0.5h) then 3.5 µg/min/kg Days 18-20 pregnancy	Fetal morphine levels x1.5 maternal plasma levels; fetal brain levels x4 maternal plasma levels.	Gabrielsson & Paalzow (1983)
	10,35,70 mg/kg/day Days 5-20	Pregnancy rate reduced signif at 35,70 mg/kg dose levels No teratogenic effects but growth retardation at 35 mg/kg.	Fujinaga & Mazze (1988)
Hamster	35-322 mg/kg s.c. single dose on Day 8	Small decrease in litter size. Above 222 mg/kg morphine, 25% fetuses with congenital abnormalities including exencephaly and cranioschisis.	Geber & Schramm (1975)
Rabbit pregnancy	2.5-10 mg/kg q6h s.c. from early No acceleration of fetal lung to delivery	Signif fetal weight loss. maturation.	Roloff et al (1975)
	50 and 100 mg/kg/day 7 days prior to mating and until day 29	Signif reductions in fetal growth, body and organ weight.	Raye et al (1977)
Sheep	0.075 to 80 mg/h infusion to fetus for 2 to 6 h.	Signif abstinence syndrome following discontinuation.	Szeto & Umans (1985)

2. Post-Natal Development

Administration of morphine to pregnant rats at 35 mg/kg/day via osmotic pump results in a significantly increased fetal mortality rate of 56% (Fujnaga & Mazze, 1988). Tolerance to the analgesic effects of morphine develops in the young of pregnant rats exposed to morphine during pregnancy (Johannesson & Becker, 1972; Steele & Johannesson, 1975). Rats exposed to morphine *in utero* develop self administration behaviour for morphine faster than controls, suggesting a tendency to develop addiction faster (Glick et al, 1977). Administration of morphine during pregnancy and lactation in rats results in retardation of body growth in offspring (Zagon & McLoughlin, 1977). The results of these studies have been considered in the Pregnancy - Category C labeling proposed for Kadian™ and the precaution recommended in the section headed Nursing Mothers. This is consistent with currently approved morphine products.

A summary of the above post-natal development studies for morphine is presented in Table 10.

Table 10. Studies of post-natal development following *in utero* exposure to morphine

	Dose / route Days of admin. Species	Results	Reference	
	Rat 20 mg/kg s.c. Days 17-20	Tolerance developed to analgesic effect of morphine in morphine exposed offspring	Johannesson & Becker (1972)	
20	20 mg/kg/day s.c. signif reduction in body wgt 20 mg/kg/day i.v. infusion at day 21 or 22	Morphine exposed offspring reduced brain wgt and lower levels of brain DNA,RNA, protein. Tolerance to morphine analgesia disappeared in 12-20 days for morphine injected group. Reverse findings for morphine infused group	Steele & Johannesson (1975)	at days 17-
mating	10-40 mg/kg i.p. bd in morphine offspring & during pregnancy/ lactation	Retardation of body growth	Zagon & McLoughlin (1977)	5 days pre-
	35 mg/kg/day via osmotic mini-pump Days 5-20	Signif higher mortality in morphine-exposed offspring (56% vs 4% controls). Lower mean neonatal weight in morphine exposed offspring	Fujinaga & Mazze (1988)	
	given in drinking water during pregnancy	offspring exposed to morphine *in utero* developed self administration behaviour ('addiction') faster	Glick et al (1977)	

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A comprehensive review of the available teratology studies related to morphine is presented by Lee and Chiang (1985). Data from this review has been presented in Section 5A in the complete report.

F. Mutagenicity Studies — NDA Volume 23

In vitro studies

Morphine is not mutagenic in *Salmonella typhimurium* TA98 as determined by plate-incorporation assay (Friesen et al, 1985).

Table 11. Mutagenicity of morphine in *Salmonella typhimurium* TA98

Compound	Specific mutagenicity in *S. typh.* TA98 (rev/µg)	
	per µl S9	at optimum S9 concentration
Morphine	0	0

In vivo studies

The results of the *in vivo* mutagenicity tests for morphine sulfate are presented in Table 12.

Table 12. Summary of *in vivo* mutagenicity studies for morphine

Test Species	Dose (route) mg/kg	Findings	Reference
Mouse			
Cytogenic Assay	3.2 to 64 (i.p.)	Chromosomal aberrations (breakages) at higher incidence than controls.	Swain et al (1980)
Micronucleus Test	3.2 to 32 (i.p.)	Significant increases in incidence of micro-nuclei in erythrocytes, indicating chromosomal breakage.	Das & Swain (1982)
Dominant Lethal Test	10,20,40,60 (i.p.)	High mutation indices particularly in early spermatid stage. Increase in number of early deaths.	Badr & Rabouth (1983)
Spermatocyte Test	10,20,40,60 (i.p.)	Chromosomal aberration frequency in morphine group 3-6 times greater than controls.	Badr & Rabouth (1983)

The labeling for Kadian™ Capsules states that studies of morphine sulfate in animals to evaluate the drug's mutagenic potential have not been conducted, recognizing the lack of GLP standard studies in the published literature.

G. Absorption, Distribution, Metabolism, Excretion (ADME) Studies

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1. Absorption

a. Gastrointestinal Absorption in Rats

Approximately 65% and 18% of the dose of morphine was excreted in the urine and feces respectively following s.c. or intragastric dosing, indicating that morphine is completely absorbed from the GI tract. However, following intragastric dosing, considerably less of the total urinary activity was associated with unchanged morphine (16% following intragastric, 41% following s.c. dosing) indicating that morphine undergoes extensive biotransformation after oral administration (Walsh & Levine, 1975).

b. Bioavailability of Morphine

The reduced analgesic effect of morphine following oral administration in comparison to parenteral administration, has been attributed to the 'first-pass effect' i.e. reduced systemic availability of drugs after oral administration even following complete absorption. Iwamoto & Klassen (1977) examined the total first-pass effect namely gastrointestinal and hepatic extraction and/or metabolism, on the pharmacokinetics of morphine after oral and portal administration to rats. Morphine 5 mg/kg was completely absorbed after oral administration and the half-life was approximately 2 hours after all routes of administration. The overall first-pass effect was 82% for morphine (18% bioavailability) with approximately 2/3 due to the extraction/metabolism in the intestine and the remaining 1/3 due to extraction by the liver.

2. Distribution

Numerous studies in animals have investigated the pharmacokinetic profile of morphine following oral and intravenous administration. Species studied include the rat, dog and monkey and the pharmacokinetic parameters of volume of distribution and plasma protein binding are summarized in Table 13. Across all studies, the results are very comparable with the volume of distribution (V_d) ranging from 1.5-6.1 L/kg in the dog. Plasma protein binding of 36 ± 1% has been reported following morphine administration (Garrett & Jackson, 1979).

Table 13. Distribution of morphine in animal pharmacokinetic studies

Parameter	Species(n)	Dose (route) mg/kg	Reference
V_d (L/kg)			
10.8 ± 1.5	rat (6)	5.0 (i.v.,oral)	Iwamoto & Klaassen (1977)
3.47 ± 1.07	rat (4)	2.5 (i.v.)	Horton & Pollack (1991)
2.2 ± 0.3	dog (8)	2.0 (i.v.)	Finck et al (1977)
2.8 - 4.7	dog (3)	7.2-7.7 (i.v.)	Garrett & Jackson (1979)
6.1 ± 0.8	dog (6)	0.3 (i.v.)	Hug et al (1981)
3.8 ± 0.9	dog (4)	2.0 (i.v.)	Hug et al (1981)
1.5 ± 0.6	dog (5)	1.0 (i.v.)	Jacqz et al (1986)
2.68 ± 3.15	monkey (3)	0.3 (i.v.) 2.0 (oral)	Rane et al (1984)
Plasma Protein Binding			
36 ± 1%	dog (3)	7.2-7.7 (i.v.)	Garrett & Jackson (1979)

Animal studies have indicated that following absorption morphine is distributed to skeletal muscle, kidney, liver, intestinal tract, lungs, brain and cardiac muscle (Sloan et al, 1991). This is similar to the distribution profile of morphine in humans. The labeling for Kadian™ Capsules indicates a V_d of 4 L/kg and plasma protein binding of 30-35% for morphine sulfate, which is in agreement with the findings of the preclinical studies.

3. Metabolism

a. Identified Metabolites

The following metabolic pathways have been reported:

Conjugation to give M-3-G, M-6-G, morphine-3,6-diglucuronide or morphine-3-ethereal sulfate.

N-demethylation to yield normorphine.

Oxidation to form dihydromorphinone.

Various metabolic pathways have been reported to give rise to the following metabolites: morphine-N-oxide, alpha-and beta-dihydromorphine, mono- and dihydroxymorphine, beta- or gamma-isomorphine and a glutathione conjugate of dihydromorphinone.

b. Species Differences in Glucuronidation

Species differences in glucuronidation of morphine hydrochloride was examined *in vivo* and *in vitro* using mice, rats, guinea pigs and rabbits (Kuo et al, 1991). Morphine-3-glucuronide was the major urinary metabolite in all species; however, a remarkable species difference was observed in urinary excretion of morphine-6-glucuronide. Table 14 summarizes the various metabolites of morphine identified in a range of animal species.

Table 14. Various metabolites of morphine reported in a variety of animal species

Metabolite	Detected in the following species								Reference
	Mouse	Rat	Rabbit	G.Pig	Dog	Cat	Monkey	Chicken	
Morphine-3-glucuronide	√	√	√	√	√	√	√	√	Yoshimura et al (1969)[a] Yeh et al (1979)
Morphine-6-glucuronide	√	√	√	√	√	-	√	√	Yoshimura et al (1969)[a] Yeh et al (1979)
Morphine-3-ethereal sulfate	-	-	-	-	-	√	-	√	Fujimoto & Haarsted (1969)
Dihydromorphinone	√	√	√	√	-	√	√	-	Yeh et al (1977)
Normorphine	√	√	√	√	√	√	√	-	Yeh et al (1977)
Morphine-N-oxide	-	-	-	√	-	-	-	-	Yeh et al (1979)
alpha & beta-dihydromorphine	-	√	√	√	-	-	-	-	Yeh et al (1979)
monohydroxymorphine	-	√	√	√	-	√	-	-	Yeh et al (1979)
dihydroxymorphine	√	±	√	-	-	-	-	-	Yeh et al (1979)
beta or gamma isomorphine	-	-	-	±	-	-	-	-	Yeh et al (1979)
(8S)- (Glutathion -S-YL) dihydromorphinone	-	-	-	√	-	-	-	-	Ishida et al (1989)[a]

a. following administration of morphine hydrochloride. All other studies used morphine sulfate.
± equivocal result

In human subjects, virtually all morphine is converted to glucuronide metabolites including M-3-G and M-6-G. Due to the extensive metabolism of morphine by the liver, it should be used with caution in patients with hepatic dysfunction since an increased bioavailability after oral administration or cumulative effects may occur. Similar caution should be exercised in renal dysfunction as M-6-G, the active metabolite may accumulate and symptoms of morphine overdose may result.

The proposed labeling for Kadian™ contains the following statement under the section headed Metabolism and Pharmacokinetics:

> The glucuronide system has a very high capacity and is not easily saturated even in disease. Studies in healthy subjects and cancer patients have shown that the glucuronide metabolite to morphine mean molar ratio (based on AUC) are similar following single doses of Kadian™ and morphine sulfate solution, and at steady state for Kadian™, controlled-release morphine sulfate tablets and morphine sulfate solution. The morphine to morphine-3-glucuronide to morphine-6-glucuronide mean molar ratios (based on AUC) are approximately 1:24:4, similar to those occurring with both morphine sulfate solution and controlled-release morphine tablets following single doses and at steady state.

4. Excretion

The various publications reviewed under the distribution of morphine also present quantitative data on elimination half-life ($t_{1/2\beta}$) and total plasma clearance which are summarized in Table 15.

Table 15. Elimination of morphine in animal pharmacokinetic studies

Parameter	Species (n)	Dose (route) mg/kg	Reference
$t_{1/2\beta}$ (min)			
approx 120	rat (6)	5.0 (i.v., oral)	Iwamoto & Klaassen (1977)
76 ± 14	rat (6)	10.0(i.v.)	Shibanoki et al (1991)
approx 65	dog(8)	2.0(i.v.)	Finck et al (1977)
83 ± 8	dog (3)	7.2 - 7.7 (i.v.)	Garrett & Jackson (1979)
25 ± 5	dog (10)	0.3 (i.v.)	Hug et al (1981)
65 ± 30	dog (5)	1.0 (i.v.)	Jacqz et al (1986)
102 - 202	monkey (3)	0.3 (i.v.) 2 .0 (oral)	Rane et al (1984)
Total Plasma Clearance (mL/min/kg)			
66.1 ± 6.9	rat (6)	5.0(i.v., oral)	Iwamoto & Klaassen (1977)
43.7 ± 3.5	rat (4)	2.5 (i.v.)	Horton & Pollack(1991)
21 - 26	dog (3)	7.2 -7.7 (i.v.)	Garrett & Jackson (1979)
51 ± 30	dog (5)	1.0 (i.v.)	Jacqz et al (1986)
34.0 ± 4.4	sheep (4)	2.5,5,10,20(i.v.)	Sloan et al (1991)
9.2 ± 21.3	monkey (3)	0.3 (i.v.) 2 (oral)	Rane et al (1984)

The labeling for Kadian™Capsules indicates an average terminal elimination half-life in humans of 2 to 4 hours, which is in agreement with the preclinical findings.

Enterohepatic recirculation and renal metabolism of morphine in the rat was also reported by Horton & Pollack (1991) and parameters of total systemic clearance, hepatic clearance and renal clearance are summarized in Table 16.

Table 16. Morphine clearance parameters from animal studies

Parameter		Species(n)	Reference Dose
Clearance	L/min	Sheep (4)	Sloan et al (1991) 2.5, 5, 10,20
Total body	= 1.63 ± 0.21		mg/hr i.v.
Hepatic clearance	= 1.01 ± 0.10 (62%)		
Renal clearance	= 0.55 ± 0.06 (35%)		
Clearance	mL/min/kg (1991)	Rat (4)	Horton & Pollack
Total body	= 55.2 ± 17.2		2.5 mg/kg i.v.
Hepatic clearance	= 31.4 ± 8.5 (56.8%)		
Renal clearance	= 5.7 (28.5%)		

In human subjects, the elimination of morphine occurs primarily as renal excretion of M-3-G; a small amount of the glucuronide conjugate is excreted in the bile and there is some minor enterohepatic recycling.

From these studies it can be concluded that the liver and kidneys account for the majority of morphine clearance and that the kidneys both excrete and metabolize morphine. Thus caution should be exercised with the clinical use of morphine in hepatic or renal dysfunction. The proposed labeling for Kadian™ Capsules contains advice to administer with caution in patients with hepatic or renal dysfunction.

APPLICATION SUMMARY

6. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SUMMARY — NDA Volume 26

Kadian™ morphine sulfate sustained-release capsules have been developed by F.H. Faulding & Co., Limited, an Australian pharmaceutical company, and are designed to provide a true sustained-release oral morphine formulation for once-a-day or twice-a-day administration in the management of moderate to severe pain where treatment with opioid analgesics is required over a period of more than a few days.

Kadian™ Capsules consist of cores acting as drug reservoirs surrounded by a dissolution rate controlling polymer membrane. The polymer coated cores (or pellets) are encapsulated into hard gelatin capsules in three dosage strengths: 20 mg, 50 mg and 100 mg.

Throughout its development, Kadian™ has been referred to by several different names. The early product code name was MOLLY. The product has also been referred to as KAPANOL® which is its trade name in other regions. In addition, Kadian™ has been designated as "Morphine Sulfate Extended-Release Capsules" by Purepac Pharmaceutical Co., of Elizabeth, New Jersey, the US contract manufacturer of Kadian™. All of these names appear at various times throughout this application and all refer to the same product.

The clinical program for Kadian™ Capsules was developed in consultation with reviewers in the FDA Pilot Drug Evaluation Staff and addresses a number of pharmacokinetic issues. Data are provided to address:

a. Oral bioavailability of Kadian™ capsules under varying circumstances (dissolution ranges and dosage ranges) and in comparison to marketed formulations of morphine (solution and controlled-release MS Contin® tablets).

b. Oral bioequivalence of Kadian™ capsules under varying conditions and against marketed comparators.

c. Single-dose (healthy volunteer) and steady-state (cancer patients) pharmacokinetics of Kadian™ and comparative pharmacokinetics with marketed comparators.

d. The effect of food on Kadian™ pharmacokinetics.

e. The effect of different scales and sites of manufacture on the pharmacokinetics of Kadian™ capsules.

f. Development of an *in vitro/in vivo* correlation model for Kadian™ capsules.

g. Investigation of pharmacokinetic-pharmacodynamic relationship for Kadian™ capsules in healthy subjects and cancer pain patients.

A total of nine studies have been conducted to characterize various aspects of the bioavailability and performance of the Kadian™ delivery system under single-dose and steady-state conditions in both healthy subjects and patients with cancer pain. A tenth study was conducted to validate the method of blinding MS Contin® tablets for a Phase III trial.

Table 1 provides a summary of all pharmacokinetics and broavailability studies for Kadian™.

Table 1. Summary of Pharmacokinetic and Bioavailability Studies

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects Treated		Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs 4) IND Serial No. (vol/page)
MOBU7/90-2 United States M. Allen Tompkins, MD	Completed Dec. 7, 1990 - Dec. 24, 1990	Single-dose, 3-way crossover study in normal volunteers	Kadian™ 50 mg [fasted] Kadian™ 50 mg [fed] Morphine Solution 25 mg [fasted]	Randomized: Completed:	30 30	23.8 ± 5.4 30 M, 0 F 29 W, 1 NW	1) **034 / 001** 2) **137 / 067** 3) 4) **037**
MOB-1/90 Australia Dr. David A Cherry	Completed April 4, 1991 - July 2, 1992	Multiple-dose, randomized, open-label, 3-way crossover study in cancer patients.	Kadian™ q12h (x 7 ± 1 days) MST Continus® q12h (x 7 ± 1 days) Morphine Solution q4h (x 7 ± 1 days)	Randomized: Completed:	34 24	64.6 ± 10.7 36 M, 14 F 50 W, 0 NW	1) **027 / 001** 2) **138 / 001** 3) **150 / 131** 4) **064**
KAP-RRC/91/01 United States M. Allen Tompkins, MD	Completed April 19, 1991 - May 25, 1991	Single-dose, 3-way crossover study in normal volunteers	Kadian™ 50 mg MST Continus® 60 mg Morphine Solution 25 mg	Randomized: Completed:	27 24	30.0 ± 7.4 27 M, 0 F 25 W, 2 NW	1) **041 / 001** 2) **037 / 001** 3) **150 / 061** 4) **058**
MOBU-9/90 United States M. Allen Tompkins, MD	Completed April 26, 1991 - May 20, 1991	Single-dose, randomized, open-label, 4-way crossover study in normal volunteers	Kadian™ 30 mg Kadian™ 50 mg Kadian™ 70 mg Kadian™ 100 mg	Randomized: Completed:	28 24	26.8 ± 7.0 28 M, 0 F 21 W, 7 NW	1) **056 / 001** 2) **137 / 130** 3) --- 4) **072**

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Summary of Pharmacokinetic and Bioavailability Studies (continued)

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects Treated		Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs 4) IND Serial No. (vol/page)
MOBU-10/90 United States M. Allen Tompkins, MD	Completed May 10 1991 - June 8, 1991	Single-dose, randomized, open-label, 3-way crossover comparison of 3 lots with differing dissolution rates in normal volunteers	Kadian™ 50 mg (faster dissolution) Kadian™ 50 mg (intermediate dissolution) Kadian™ 50 mg (slower dissolution)	Randomized: Completed:	24 24	27.0 ± 7.5 24 M, 0 F 24 W, 0 NW	1) **050 / 001** 2) **137 / 197** 3) --- 4) **068**
083-031 United States Merlin Kampfer, MD	Completed Feb. 29, 1992 - March 15, 1992	Single-dose, randomized, 2-way crossover study to validate method of blinding for Phase II/III clinical trials. Conducted in normal volunteers	MS Contin® Tablet 60 mg MS Contin ® Tablet 60 mg in a titanium dioxide capsule	Randomized: Completed: Evaluable:	16 11 10	28.8 ± 7.8 16 M, 0 F 16 W, 0 NW	1) **047 / 001** 2) **137 / 300** 3) **150 / 001** 4) **082**
MOR-8/92 United States James C. Kisicki, MD	Completed Nov. 20, 1992 - Dec. 20, 1992	Single-dose, randomized, 4-way crossover comparison of 4 batches with differing dissolution rates. Conducted in normal volunteers	Kadian™ 50 mg (faster batch 1) Kadian™ 50 mg (faster batch 2) Kadian™ 50 mg (slower dissolution) Kadian™ 50 mg (intermediate dissolution)	Randomized: Completed:	16 16	26.8 ± 8.0 16 M, 0 F 15 W, 1 NW	1) **053 / 001** 2) **137 / 240** 3) --- 4) **069**

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Summary of Pharmacokinetic and Bioavailability Studies (continued)

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects Treated		Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs 4) IND Serial No. (vol/page)
MOR-2/92 United States R.K. Portenoy, MD K. M. Foley, MD	Study terminated prior to completion due to poor recruitment & control of procedures. January 29, 1993 - December 19, 1993	Multiple-dose, randomized, double-blind, double-dummy, balanced incomplete block crossover design in cancer patients with moderate to severe pain.	Two of Three: Kadian™ q24h (x 4-7 days) Kadian™ q12h (x 4-7 days) MS Contin® q12h (x 4-7 days)	Randomized: Completed: Evaluable:	19 16 6	47.5 (23 - 71) 7 M, 12 F 17 W, 2 NW	1) **076 / 001** 2) **147 / 174** 3) **157 / 001** 4) **087**
MOR-13/94 Australia Dr. Alan F. Broomhead	Completed Nov. 30, 1994 - Dec. 16, 1994	Single-dose, 3-way crossover study in normal volunteers	Kadian™ 50 mg: Australia Commercial-scale batch Australia Pilot-scale batch US Commercial Test-scale batch	Randomized: Completed:	36 34	22.4 ± 4.4 36 M, 0 F 35 W, 1 NW	1) **044 / 001** 2) **137 / 267** 3) **---** 4) **089**
MOR-9/92 Australia Dr. David A. Cherry	Completed, July 15, 1993 - Dec. 30, 1994	Multiple-dose, randomized, double-blind, double-dummy, two-way crossover in cancer patients with moderate to severe chronic pain	Kadian™ q24h (x 7 ± 1 days) MS Contin® q12h (x 7 ± 1 days)	Randomized: Completed: Evaluable:	29 25 24	64.9 ± 13.2 18 M, 11 F 29 W, 0 NW	1) **077 / 001** 2) **140 / 001** 3) **155 / 192** 4) **092**

000174

A. DRUG FORMULATION NDA Volume 26

For a full description of the drug formulation, manufacturing methods, clinical batch records and specifications, refer to the Chemistry, Manufacturing, and Controls section of this NDA.

Kadian™ was developed by Faulding, an Australian pharmaceutical company, to be a sustained-release morphine sulfate product, suitable for once or twice daily administration. It consists of a core acting as a drug reservoir surrounded by a dissolution rate controlling polymer membrane. The coated cores (pellets) are encapsulated into hard gelatin capsules in three dosage strengths; 20 mg, 50 mg, and 100 mg. The same core and pellet formulation is used for all dosage strengths with differing numbers of pellets being used to control the dosage strength.

The rate of release of morphine sulfate from the core is controlled by the polymer coating which consists of:

- an insoluble polymer component (ethylcellulose),
- an enteric polymer component (methacrylic acid copolymer which is insoluble and relatively hydrophobic at pH 1.2),
- a water soluble component (polyethylene glycol, which is soluble and hydrophilic at pH 1.2) and,
- a water insoluble plasticiser (diethyl phthalate).

At pH 1.2, approximating that in the human stomach, the hydrophilic component of the coating dissolves and allows water to diffuse into the core containing morphine sulfate. The dissolved active (i.e., morphine sulfate) diffuses out through the coating. The dissolution profile is essentially linear at this pH.

At higher pH's, approximating those in the human intestine, both the hydrophilic and enteric components of the coat dissolve. Thus, the rate of dissolution of morphine sulfate from the core is greater at pH's above 5.5.

All raw materials used in Kadian™ are pharmaceutical grade and conform to established pharmacopeal specifications. The concentrations in the formulation, individually or in combination, administered with standard dosage regimens, are not expected to cause concern with respect to acute or chronic toxicity.

The known related substances found in the morphine sulfate raw material available in the US and used in Kadian™ are 10-alpha hydroxymorphine, morphine-N-oxide, pseudomorphine and a recently identified oxidation

product 6-oxo morphine (previously referred to as "unknown 1"). These related substances have been isolated and adequate controls are in place to ensure that their levels are not significantly increased during manufacturing and storage.

The formulation excipients and morphine sulfate related substances are present in similar quantities in a large number of already marketed products in the U.S. and are apparently of low inherent toxicity and are present in such small amounts so as not to be clinically significant. All formulation excipients are listed in the Division of Drug Information Resources, October 1993, Inactive Ingredients Guide issued by FDA, CDER, Office of Management.

The manufacture of Kadian™ capsules is comprised of six major stages. These are granulating solution manufacture, core manufacture, coating solution manufacture, pellet manufacture, encapsulation and packaging.

Core manufacture consists of slurry coating by rotorgranulation in a fluid bed of morphine sulfate of defined particle size onto seed cores (sugar spheres) of defined size range. A granulating solution of hydroxypropyl methylcellulose dissolved in alcohol/water is used as the binding agent and vehicle. Homogeneity of the dispersed morphine sulfate in the granulation solution as it is applied to the seed cores is facilitated by continuous low shear stirring. Solvent is continuously evaporated during the slurry coating process. On complete application of the morphine sulfate slurry, the cores are dried in the same vessel.

The core batch is sieved to a defined size range. Undersized and oversized cores are discarded to ensure batch to batch uniformity. QC testing is conducted at this intermediate stage. Batches of cores meeting specification are released for the spray coating stage.

Pellet manufacture consists of controlled application of the polymer coating solution to cores in a fluid bed equipped with a Wurster insert. The polymers and plasticiser are dissolved in alcohol and talc is added prior to commencement of the coating process. The homogeneity of the talc/coating solution suspension during the spraying process is facilitated by continuous stirring.

The coating process may be done in several stages. In-process samples of pellets are taken after a main spray and dissolution testing checks the progress toward meeting the desired drug release specification. The amount of adjustment or final spray is calculated and after this is applied, the pellets are dried to remove the solvent. The pellets are then tested to the in-process specification.

If the pellets meet specification, they are dusted with talc in the fluid bed to improve flowability and reduce the effect of electrostatic charge during encapsulation. The batch is screened to the appropriate size range, then sampled and tested for conformity to in-process specifications prior to encapsulation and packaging.

Pellets may be blended in the fluid bed prior to encapsulation to achieve the appropriate batch size.

B. Single-Dose Trials in Healthy Subjects — NDA Volume 26

Seven (7) single-dose randomized, crossover studies were conducted in healthy subjects. These studies included investigations of:

1) the bioavailability of Kadian™ with respect to an immediate-release oral solution and an approved controlled-release product (MST Continus®/ MS Contin®);

2) the effect of food on Kadian™ bioavailability;

3) pharmacokinetic linearity and dose-proportionality after increasing Kadian™ doses;

4) *in vitro - in vivo* correlations;

5) the bioequivalence of Kadian™ batches manufactured at different scales and at different sites (Australia and USA);

6) and the effect on bioavailability of placing an MS Contin® tablet in an opaque capsule for use in blinded clinical studies.

The following table provides a summary of the design and objectives of the bioavailability and bioequivalence studies conducted.

Table 2: Summary of Bioavailability and Bioequivalence Studies

Study Number	Design	Treatments	Features
MOB-1/90[a]	multiple-dose 3-way crossover n = 24 Patients	Kadian™ q12h MST Continus® q12h IR Solution q4h	Steady-state comparison of morphine bioavailability relative to a marketed product and oral solution in patients with chronic cancer pain. Subgroup analysis of molar metabolite ratios.
MOBU7/90-2[b]	single-dose 3-way crossover n = 30 Healthy volunteers	Kadian™ 50mg [fasted] Kadian™ 50mg [fed] IR Solution 25mg [fasted]	Single-dose evaluation of the effect of food (a high-fat breakfast) on morphine bioavailability, and relative bioavailability in comparison with an oral solution. Subgroup analysis of molar metabolite ratios.
KAP-RRC/91/01[b]	single-dose 3-way crossover n = 24 Healthy volunteers	Kadian™ 50mg MST Continus® 60mg IR Solution 25mg	Single-dose comparison of morphine bioavailability relative to a marketed product and oral solution.
MOR-13/94[c]	single-dose 3-way crossover n = 34 Healthy volunteers	Kadian™ 50mg: AUS Commercial-scale AUS Pilot-scale batch US Mid-scale batch	Single-dose bioequivalence comparison of 3 batches produced in Australia and the United States to evaluate effect of scale-up and production in different manufacturing sites.
083-031[b]	single-dose 2-way crossover n = 11 Healthy volunteers	MS Contin® 60mg MS Contin® 60mg in a titanium dioxide capsule	Single-dose bioequivalence evaluation of the effect of placing an MS Contin® tablet within an opaque, white capsule (TiO_2). Conducted to validate method of blinding for Phase II/III clinical trials.

[a] Study conducted at Pain Management Unit, Flinders Medical Center, Bedford Park, South Australia
[b] Study conducted at Harris Laboratories, Inc., USA
[c] Study conducted at Faulding Drug Studies Unit (Clinical), Royal Adelaide Hospital, Adelaide, South Australia
IR = immediate-release
MST Continus® (morphine sulfate controlled-release, Napp Laboratories, Cambridge, UK, the European and Australian trade name for MS Contin®)
MS Contin® (morphine sulfate controlled-release, Purdue Frederick, Norwalk, CT USA)
Kadian™ (morphine sulfate sustained-release capsules, F.H. Faulding & Co. Limited, Adelaide, South Australia)

Two studies MOBU-10/90 and MOR-8/92 examined the relationship between the *in vitro* dissolution rates and *in vivo* biovailability of Kadian™. An eight healthy subject study, MOBU-9/90, demonstrated that Kadian™ Capsules demonstrate linear pharmacokinetics over the dose range 30 mg to 100 mg.

The results of the seven single-dose trials are summarized in the following table:

Table 3: Summary of Mean[1] Single-Dose Pharmacokinetic Data

Study	Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	WIDTH (hr)
MOBU7/90-2	Kadian™ 50mg (fasted)[2]	4.06	8.47	63.38[a]	6.70
	Kadian™ 50mg (fed)[2]	3.61	10.13	65.67[a]	8.27
	Solution 25mg (fasted)[2]	15.89	0.96	59.37[a]	0.94
KAP-RRC/91/01	Kadian™ 50mg[2]	3.90	8.58	67.75[a]	6.29
	MST Continus® 60mg[2]	7.63	2.46	76.07[a]	2.46
	Solution 25mg[2]	16.11	0.88	90.69[a]	1.17
MOR-13/94	Kadian™ 50mg [A]	11.10	7.57	137.42[b]	3.98
	Kadian™ 50mg [B]	10.19	7.80	137.27[b]	4.97
	Kadian™ 50mg [C]	10.61	8.10	134.38[b]	4.67
MOBU-10/90	Kadian™ 50mg (HDR)	10.20	6.71	137.64[a]	4.07
	Kadian™ 50mg (MDR)	7.88	7.58	139.99[a]	6.00
	Kadian™ 50mg (LDR)	6.11	12.29	136.83[a]	12.37
MOR-8/92	Kadian™ 50mg (HDR 1)	10.48	7.06	138.49[b]	5.20
	Kadian™ 50mg (HDR 2)	8.79	8.75	134.55[b]	7.83
	Kadian™ 50mg (CDR)	8.85	8.38	135.75[b]	5.27
	Kadian™ 50mg (SDR)	7.54	8.88	131.62[b]	8.01
MOBU-9/90	Kadian™ 30mg	4.55[3]	7.79	81.75[a,3]	7.33
	Kadian™ 50mg	7.81[3]	7.21	136.33[a,3]	6.32
	Kadian™ 70mg	12.69[3]	8.42	196.99[a,3]	5.66
	Kadian™ 100mg	17.78[3]	8.42	273.65[a,3]	5.01
083-031	MS Contin® 60mg (TiO_2)	15.56	2.42	131.64	-
	MS Contin® 60mg	14.49	2.35	139.50	-

[a] AUC_{0-48}
[b] AUC_{0-36}
[1] Least-square means
[2] C_{max} & AUC_{0-t} adjusted to 25 mg dose
[3] Arithmetic means
HDR - high dissolution rate
MDR - medium/central dissolution rate
LDR - low dissolution rate
[A] Australian Pilot-Scale Batch
[B] Australian Commercial-Scale Batch
[C] US Mid-Scale Commercial Test Batch
HDR 1 - high dissolution rate 1
HDR 2 - high dissolution rate 2
CDR - central dissolution rate
SDR - slow dissolution rate
(TiO_2) - encapsulated in an opaque white (TiO_2) capsule

The plasma concentrations and concentration-derived parameters (e.g., AUC_{0-t} and C_{max}) were adjusted to a 25 mg dose in the two single-dose studies that included an immediate-release solution (MOBU7/90-2 and KAP-RRC/91/01).

While it is generally considered more appropriate to compare $AUC_{0-\infty}$ values between treatments in single-dose studies, the majority of bioequivalence/bioavailability comparisons were made on the basis of AUC_{0-t} values due to the fact that half-life could not be determined for a number of subjects. Within the individual studies, it was apparent that any observed differences between $AUC_{0-\infty}$ values were a reflection of differences in estimates of the extrapolated area due to differences in the estimates of the terminal elimination rate constant. Examination of the AUC_{0-t} values across the studies that had different durations of sample collection would appear to further validate this conclusion. There are no apparent differences in the observed mean AUC_{0-t} values between study MOBU-10/90 (which measured AUC_{0-48}) and studies MOR-13/94 or MOR-8/92 (which measured AUC_{0-36}). Since the additional 12 hours of sample collection (from 36 to 48 hours) did not appear to add any appreciable area, it seems reasonable to conclude that absorption is complete by 36 hours and that comparison of the measured AUC through 36 or 48 hours is a true reflection of the extent of morphine delivery and absorption.

Study MOBU7/90-2 also studied the concentration-time profiles and molar ratios of morphine, morphine-3-glucuronide and morphine-6-glucuronide following single doses of Kadian™ fasting and fed, in a subgroup of seven subjects. The results are shown in Table 4..

Table 4: Mean Dose-Adjusted Morphine, Morphine-3-Glucuronide and Morphine-6-Glucuronide Pharmacokinetic Data From a Subgroup of Seven Subjects (Study MOBU7/90-2)

Parameter[1]	Species	Kadian™ 50 mg [fasted]	Kadian™ 50 mg [fed]	Solution 25 mg [fasted]
C_{max} (ng/mL)	morphine	5.51	4.09	18.96
	M3G	314.70	199.50	585.80
	M6G	86.30	47.30	155.10
T_{max} (hr)	morphine	8.29	9.71	1.05
	M3G	7.00	10.29	1.50
	M6G	7.00	8.86	1.64
AUC_{0-48} (ng•hr/mL)	morphine	74.03	75.57	73.61
	M3G	3182.90	3200.70	2451.60
	M6G	671.40	653.50	593.20
Molar Ratio (AUC)[2]	morphine	1.0	1.0	1.0
	M3G	32.5	29.4	27.1
	M6G	8.3	7.0	6.7
WIDTH (hr)	morphine	3.89	9.68	1.07
	M3G	5.04	7.44	1.47
	M6G	3.69	7.54	1.46

M3G = morphine-3-glucuronide
M6G = morphine-6-glucuronide
[1] concentrations and concentration-derived parameters adjusted to 25 mg
[2] M3G or M6G:morphine ratio of AUC values after conversion to nmol•hr/mL from ng•hr/mL

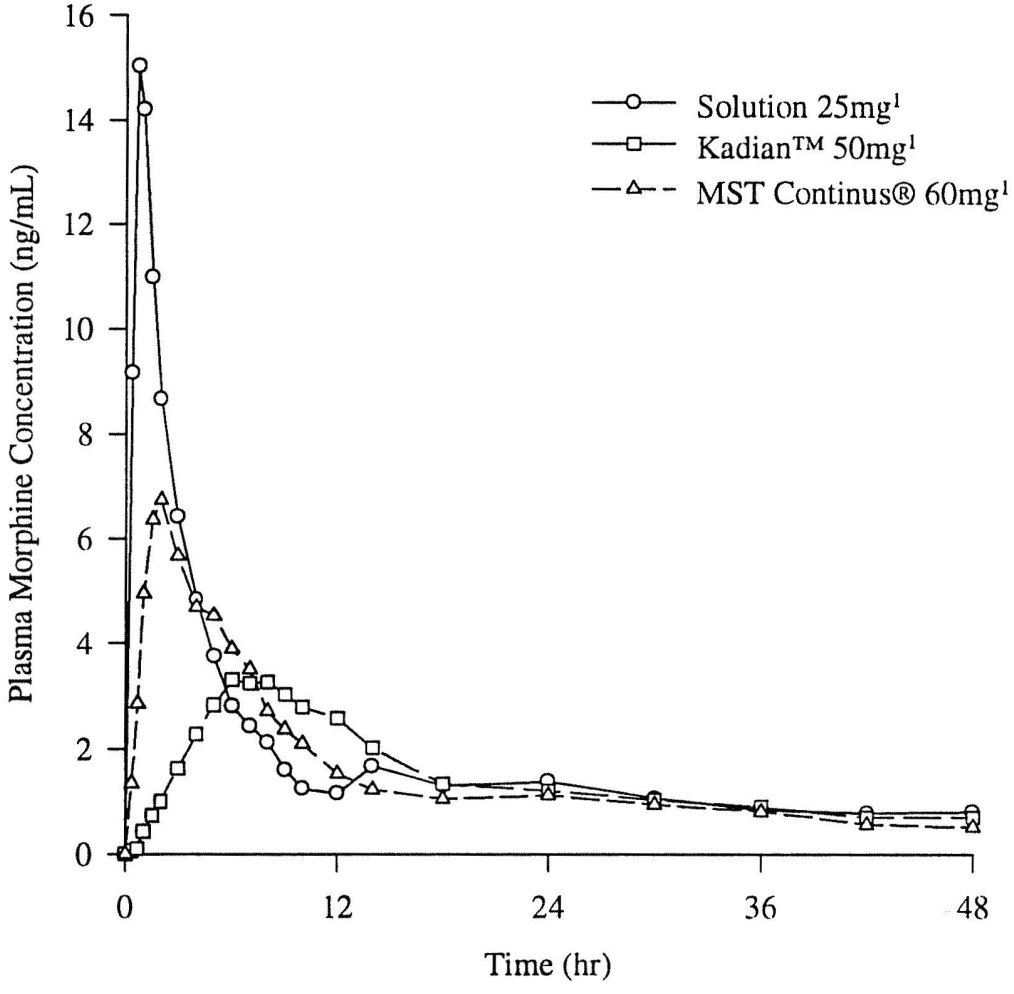
The concentrations of M3G and M6G in plasma ran in parallel to the corresponding morphine concentrations. Both metabolites reached peak concentrations at about the same time as morphine and showed a similar duration above 75% of the C_{max} concentration. There were no statistically significant differences between the three treatment groups in the molar ratios of M3G:morphine or M6G:morphine.

The pharmacodynamic data and correlations with plasma morphine concentrations obtained from this study are discussed in the section on pharmacokinetic-pharmacodynamic correlations, later in this document.

Study KAP-RRC/91/01 compared the pharmacokinetic profiles of single oral doses of Kadian™ with MS Contin® and immediate-release morphine sulfate solution.

Figure 1 illustrates that the three formulations exhibited distinctly different characteristics.

Figure 1: Dose-Adjusted[1] Morphine Plasma Concentrations (Study KAP-RRC/91/01)



[1] **plasma concentrations are adjusted to a 25 mg dose**

The Kadian™ formulation is characterized by a slower rate of absorption than either the immediate-release solution or MST Continus®. This is reflected in a longer mean T_{max} (8.58, 2.46, and 0.88 hours for Kadian™ in comparison to MST Continus®, and the oral solution, respectively) and lower mean (adjusted to a 25 mg dose) C_{max} (3.90, 7.63, and 16.11 ng/mL for Kadian™ in comparison to MST Continus®, and the oral solution, respectively).

Study MOR-13/94 compared the rate and extent of absorption of morphine, in the fasting state, from three (3) batches of a sustained-release morphine formulation (Kadian™ capsules) manufactured at different scales (Pilot-scale, Mid-scale, and Commercial-scale production batches) and at different Faulding sites (Australia vs. USA). The three batches of Kadian™ capsules were:

A. Pilot-scale batch manufactured in Australia;

B. Commercial-scale production batch manufactured in Australia; and

C. Mid-scale commercial test batch manufactured in the USA.

Both of the batches manufactured in Australia are representative of the product used in clinical trials. In addition, the commercial-scale batch (B) was manufactured in the commercial production facility utilizing full-scale equipment. The batch manufactured in the US is representative of anticipated initial commercial production.

Table 5 illustrates the different scales of production tested in MOR-13/94.

Table 5: Kadian™ 50 mg Test Formulations (Study MOR-13/94)

Treatment	Description	Capsule Batch No.	Capsule Batch Size	Pellet Batch No.	Pellet Batch Size
A	Australian Pilot-scale Batch	4029008	4,183	4016001	11.77 kg
B	Australian Commercial-scale Batch	4070045	102,789	4101005	151.86 kg
C	US Mid-scale Commercial Test Batch	PI-830	192,440	IB-015 + IB-013	70.52 kg 66.55 kg

Treatment A, the Australian Pilot-scale batch, was considered the reference product, while Treatments B and C were considered to be the test products. The Australian batches were manufactured by F. H. Faulding & Co. Limited, at its Salisbury manufacturing facility. The US batch was manufactured by Purepac Pharmaceutical Company at its Elizabeth, New Jersey facility. Purepac is a majority-owned and controlled subsidiary of Faulding and will contract manufacture Kadian™ for the US market.

The morphine pharmacokinetic parameters, obtained from the 34 subjects who completed the trial, for the three Kadian™ production batches are summarized in the following table.

Table 6: Mean[1] Morphine Pharmacokinetic Parameters Following Administration of Three Kadian™ Production Batches (Study MOR-13/94)

Parameter	[A] Australian Pilot-Scale	[B] Australian Commercial-Scale	[C] USA Mid-Scale
C_{max} (ng/mL)	11.099	10.188	10.606
T_{max} (hr)	7.573	7.802	8.104
AUC_{0-36}(ng•hr/mL)	137.424	137.269	134.378
$AUC_{0-\infty}$ (ng•hr/mL)	185.821	203.924	193.941
λ_n (hr^{-1})	0.046	0.040	0.042
$T_{1/2}$ (hr)	17.453	21.117	20.716
WIDTH (hr)	3.979	4.972	4.674
ln-C_{max} (ng/mL)	2.356	2.261	2.296
ln-AUC_{0-36} (ng•hr/mL)	4.885	4.888	4.864
ln- $AUC_{0-\infty}$ (ng•hr/mL)	5.186	5.259+	5.228

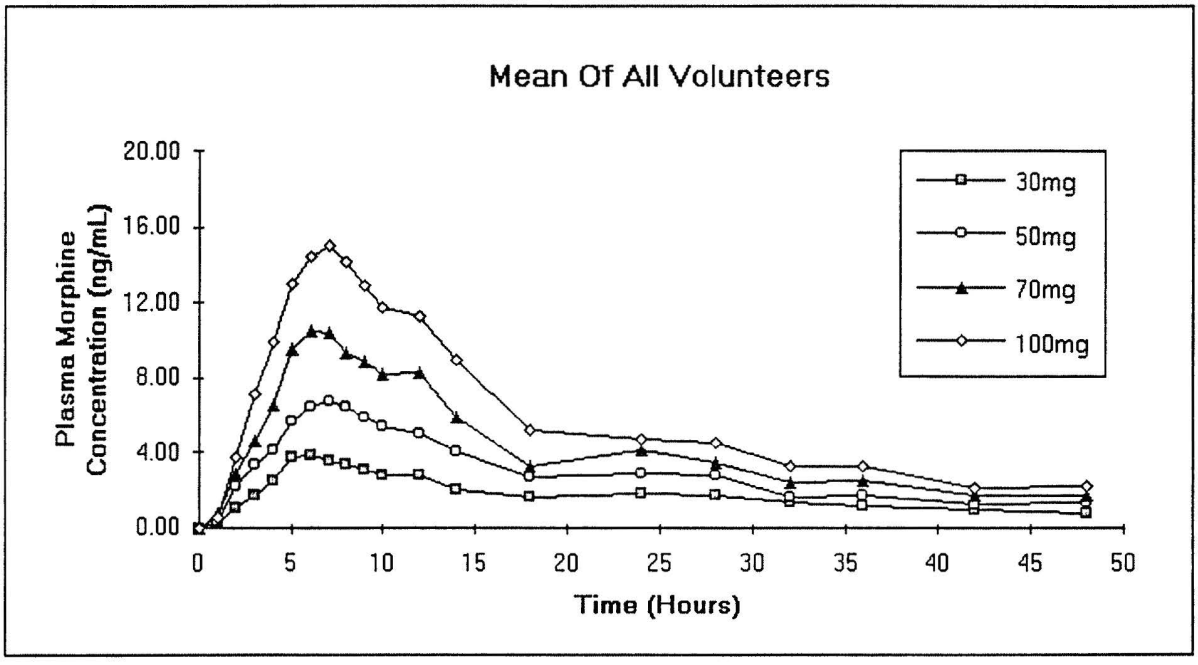
[1] Least-square means

The results of this study show that all three batches of Kadian™, a pilot-scale batch produced in Australia, a commercial-scale batch produced in Australia, and a mid-scale commercial test batch produced in the United States, are bioequivalent. This study confirms that different sized batches, produced in different plants, are bioequivalent *in vivo* when manufactured to meet the *in vitro* dissolution specifications proposed in this application. The results also confirm the successful scale-up of production from pilot-scale to commercial-scale production batches.

Study MOBU-9/90 evaluated whether Kadian™ Capsules demonstrate linear pharmacokinetcs over the dose range 30 mg to 100 mg.

Figure 2 shows that the plasma concentration of morphine increases progressively as dosage increases from 30 to 100 mg. The characteristic shape of the profiles, including the absorption and elimination phases were essentially identical at each dosage level.

Figure 2: Average Morphine Plasma Concentrations Versus Time (Study MOBU-9/90)



In order to assess whether the pharmacokinetics of morphine were linear and dose-proportional across the dosage range from 30 to 100 mg, the pharmacokinetic parameters were adjusted to the 30 mg dosage and compared across groups using analysis of variance.

Table 7: Comparison of Dose-Adjusted[1] Pharmacokinetic Parameters[2] Across the Dosage Range From 30 to 100 mg (Study MOBU9/90)

Parameter	30 mg	50 mg	70 mg	100 mg	P-value[3]
C_{max} (ng/mL)	4.55	4.69	5.44	5.33	0.0517
T_{max} (hr)	7.79	7.21	8.42	8.42	0.5363
AUC_{0-48} (ng•hr/mL)	81.75	81.80	84.42	82.10	0.7651
$AUC_{0-\infty}$ (ng•hr/mL)	108.49	105.07	104.69	101.68	0.4639
λ_n (hr^{-1})	0.0401	0.0447	0.0469	0.0431	0.4690
WIDTH (hr)	7.33	6.32	5.66	5.01	0.4679
ln-C_{max} (ng/mL)	1.440	1.490	1.639	1.614	0.0355
ln-AUC_{0-48} (ng•hr/mL)	4.374	4.379	4.411	4.379	0.7279
ln- $AUC_{0-\infty}$ (ng•hr/mL)	4.658	4.619	4.615	4.586	0.3587

[1] Values adjusted to 30 mg dose
[2] Results presented are least square-means from ANOVA
[3] P-value from ANOVA, Type-III model effects testing for differences between treatments.

The analysis of dose-adjusted pharmacokinetic parameters did not reveal any significant differences in the extent of morphine absorption or elimination with increasing dosage of the Kadian™ formulation. The only statistically significant finding was a slight increase in C_{max} at the two higher doses (70 and 100 mg). While this difference reached statistical significance for the ln-transformed results, the finding is of doubtful relevance since the magnitude of the difference represents only about 1 ng/mL on average. Considering the results for AUC and T_{max}, the observed difference in C_{max} does not appear related to either an increase in bioavailability or more rapid release, suggesting that the result is only a chance finding.

The results of this study demonstrate that the pharmacokinetics of morphine are linear and dose-proportional following administration of Kadian™ in single doses ranging from 30 to 100 mg.

Overall, the results of the single-dose trials established the following:

1. The Kadian™ sustained-release delivery system does not alter the oral bioavailability of morphine. This conclusion is supported by the results of studies MOBU7/90-2, which showed that the extent of morphine bioavailability from Kadian™ capsules is equivalent to an immediate-release oral solution, the most bioavailable form of oral morphine. Furthermore, studies MOBU-10/90 and MOR-8/92 demonstrated that wide ranges of dissolution rates for Kadian™ do not alter oral bioavailability.

2. Administration of Kadian™ immediately following a high-fat meal does not alter the performance of the delivery system. The results of study MOBU7/90-2

demonstrated that administration of Kadian™ with food does not result in dose-dumping, or any loss of the sustained-release characteristics of the formulation.

3. The plasma morphine pharmacokinetic profile following administration of Kadian™ meets the criteria for a sustained-release delivery system in comparison to both an immediate-release solution and a marketed slow-release product (MST Continus®/MS Contin® tablets). The results of studies MOBU7/90-2 and KAP-RRC/91/01 established that Kadian™ produces significantly lower C_{max} values, longer T_{max} values, and maintains the plasma morphine concentrations at a level at or above 75% of the C_{max} value for a longer period of time than either the immediate-release solution or MST Continus® tablets.

4. Batches of Kadian™ manufactured at different scales and in different manufacturing facilities are bioequivalent when produced under the proposed manufacturing methods and controls, and to the proposed dissolution specifications. The results of study MOR-13/94 showed that three different batches of Kadian™, a pilot-scale batch produced in Australia, a commercial-scale batch produced in Australia, and a mid-scale commercial test batch produced in the United States, were bioequivalent. In direct pair-wise comparisons (US mid-scale vs. Australian commercial-scale, Australian pilot-scale vs. Australian commercial-scale, and US mid-scale vs. Australian pilot-scale), the 90% confidence intervals for ln-transformed values of C_{min}, AUC_{0-36}, and $AUC_{0-\infty}$ were all well within the criteria for acceptance of bioequivalence. This study confirmed that different sized batches, produced in different plants, are bioequivalent *in vivo* when manufactured to meet the specifications proposed in this application. The results also confirmed the successful scale-up of production from pilot-scale to commercial-scale production batches. Considering these results, it is reasonable to conclude that product manufactured in the United States would be expected to match the *in vivo* performance of the product tested in clinical trials.

5. Slowing the rate of morphine delivery with Kadian™ does not affect the metabolism of morphine. The results of study MOBU7/90-2 demonstrated that the molar plasma concentration ratios of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) are unaffected by Kadian™ under fed or fasting conditions in comparison to an immediate-release solution. The molar AUC ratios of morphine:M3G:M6G were 1:33:8, 1:29:7 and 1:27:7 for Kadian™ under fasting and fed conditions, and the immediate-release solution under fasting conditions, respectively.

6. Plasma morphine pharmacokinetics are linear following administration of increasing single doses of Kadian™ over the range of 30 to 100 mg. The

results of study MOBU-9/90 demonstrated that there are no significant differences in the rate of absorption or elimination of morphine across this dosage range, and the extent of absorption increases in direct proportion to the Kadian™ dose.

C. Multiple-Dose Studies in Patients with Chronic Cancer Pain — NDA Volume 26

Three (3) multiple-dose, steady-state, randomized, crossover studies were conducted in patients with chronic cancer pain. These studies included investigations of steady-state morphine pharmacokinetics:

1) following administration of Kadian™ every 12 hours in comparison to every 12 hour administration of MST Continus® tablets and every 4 hour administration of an immediate-release solution;

2) following administration of Kadian™ every 12 or 24 hours in comparison to MS Contin® tablets administered every 12 hours; and

3) following administration of Kadian™ every 24 hours in comparison to administration of MS Contin® tablets every 12 hours. One of the studies (MOR-2/92) was terminated early due to slow enrollment of patients and poor protocol compliance. As a result, meaningful pharmacokinetic data are available from two of the studies (MOB-1/90 and MOR-9/92). The results obtained from these studies are summarized in the following table.

Table 8: Summary of Mean[1] Dose-Adjusted[2] Multiple-Dose Pharmacokinetic Data

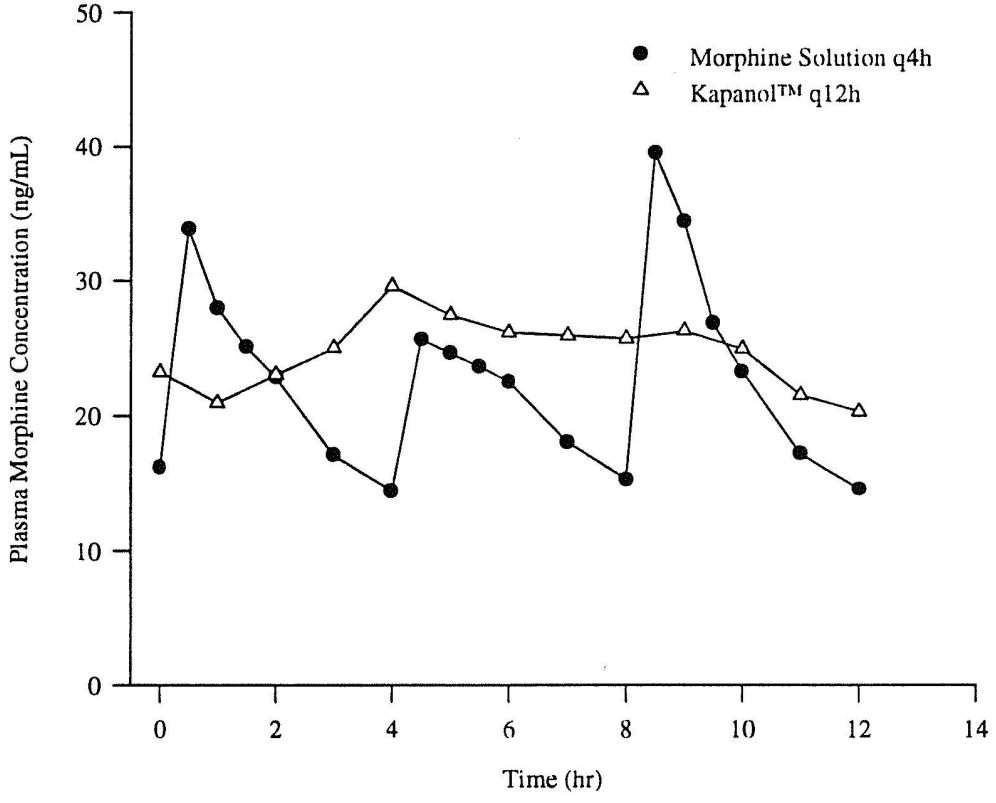
Study	Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{ss} (ng•hr/mL)	C_{min} (ng/mL)	FLUCT 1	FLUCT 2	WIDTH (hr)
MOB-1/90	Kadian™ q12h	32.1	5.7	297.66	17.7	0.9	0.6	9.1
	MST Continus® q12h	42.3	3.4	272.42	9.2	4.3	1.5	3.1
	Solution	48.3	0.7	267.58	12.4	3.7	1.7	-
MOR-9/92	Kadian™ q24h	37.3	10.3	500.89	9.9	3.0	1.4	6.0
	MS Contin® q12h	36.9	4.4	457.28 [a]	7.6	4.1	1.6	4.8

[1] Least-square means
[2] concentrations and concentration-derived parameters adjusted to a dosage of 100mg per day.
[a] AUC_{0-24}

The results of study MOB-1/90 demonstrated that Kadian™ capsules exhibit a distinctly different plasma concentration profile as compared to both the solution and MST Continus® tablets. Kadian™ capsules produce a lower C_{max} value, a longer T_{max}, a higher C_{min}, and lower fluctuation indices than either the solution or MST Continus® tablets. By direct comparison, both Kadian™ and MST Continus® were

bioequivalent to the solution and each other, only with respect to the extent of absorption (as measured by the AUC_{ss}). Beyond that, there were few similarities between Kadian™ and MST Continus®. In fact, the MST Continus® tablet was quite similar to the solution, with the exceptions that the MST Continus® tablet had significantly lower C_{min} and C_{max} values. In contrast, Kadian™ is characterized by significantly lower C_{max} values, higher C_{min} values, and lower fluctuation indices than either of the other two products; indicating that Kadian™ produces a more constant morphine plasma level and lower peak-to-trough fluctuation. Figures 3 and 4 illustrate these findings. There were also no significant differences between the three products with respect to the molar AUC ratios for morphine, morphine-3-glucuronide, and morphine-6-glucuronide.

Figure 3: **Dose-Adjusted[1], Mean Morphine Plasma Concentrations at Steady-State - Kadian™ vs. Solution, N = 24 (Study MOB-1/90)**



[1] **concentrations adjusted to a dosage of 100 mg per 24 hours.**

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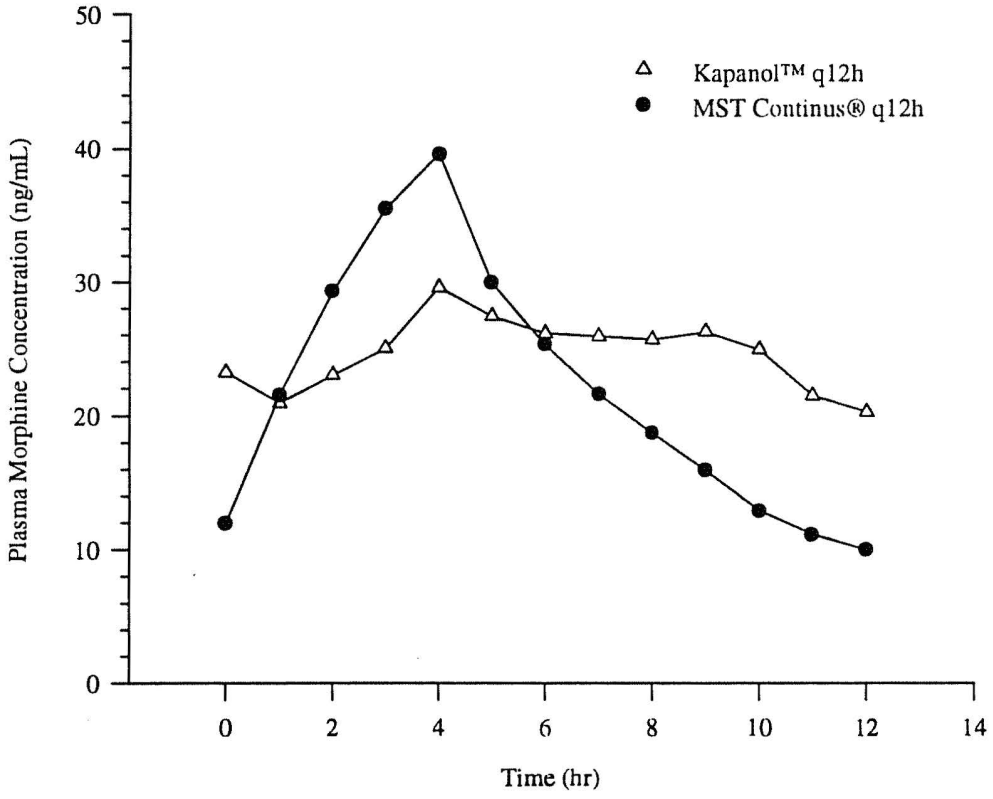
Figure 4: **Dose-Adjusted[1], Mean Morphine Plasma Concentrations at Steady-State - Kadian™ vs. MST Continus®, N = 24 (Study MOB-1/90)**



[1] **concentrations adjusted to a dosage of 100 mg per 24 hours.**

Study MOR-1/90 was also designed to study the steady-state concentrations of morphine, morphine-3-glucuronide, and morphine-6-glucuronide in plasma from at least six of the 24 evaluate patients.

Table 9 provides a comparison of AUC_{ss} and ratios of morphine and the two metabolites.

Table 9: **Comparison of AUC_{ss} and Ratios for Morphine, Morphine-3-Glucuronide, and Morphine-6-Glucuronide (Study MOB-1/90)**

Parameter		Solution	MST Continus®	Kadian™
Morphine	AUC_{ss} (ng•hr/mL)	270	266	285
	Ratio	1.0	1.0	1.0
M3G	AUC_{ss} (ng•hr/mL)	10,996	11,509	10,830
	Ratio	25.9	27.1	24.4
M6G	AUC_{ss} (ng•hr/mL)	1854	1878	1811
	Ratio	4.3	4.4	4.0

There were no statistically significant differences for the AUC_{ss} values or ratios among the three treatments for either the parent or metabolites. These data indicate that there were no significant alterations in the metabolism of morphine resulting from the differences in rate of delivery.

The results of study MOR-9/92 revealed that Kadian™ administered once daily delivered an equivalent amount of morphine to MS Contin® administered twice daily. The C_{max} value following administration of Kadian™ once daily was equivalent to the C_{max} following administration of MS Contin® twice daily even though the Kadian™ dose was twice the 12-hourly MS Contin® dose. The reduced peak-to-trough fluctuation in morphine plasma concentrations following Kadian™ administration was further characterized by lower fluctuation indices and higher C_{min} values. In addition, once daily Kadian™ administration was associated with a longer T_{max} and plasma morphine concentrations were maintained at or above 75% of the C_{max} (WIDTH) for a longer period of time than was observed after twice daily administration of MS Contin®. There were no significant differences with respect to the molar AUC ratios for morphine, morphine-3-glucuronide, and morphine-6-glucuronide between Kadian™ administered once daily and MS Contin® administered twice daily.

Overall, the results of the multiple-dose, steady-state studies in patients demonstrated the following:

1. The extent of morphine absorption following administration of Kadian™ every 12 hours is equivalent to the extent of morphine absorption following administration of an oral solution every four hours.

2. Administration of Kadian™ every 12 hours is equivalent to administration of MS Contin® every 12 hours with respect to the extent of morphine absorption; however, Kadian™ shows a more enhanced sustained-release profile than MS Contin® as evidenced by significantly lower C_{max} values, longer T_{max} values, higher C_{min} values, and lower fluctuation indices.

3. Administration of Kadian™ once every 24 hours is equivalent to administration of MS Contin® every 12 hours with respect to the extent of morphine absorption; however, Kadian™ shows a more enhanced sustained-release profile than MS Contin® as evidenced by significantly longer T_{max} values, higher C_{min} values, and lower fluctuation indices.

4. Slowing the rate of morphine delivery with the Kadian™ delivery system does not alter the metabolism of morphine in patients.

5. The plasma morphine pharmacokinetic profiles following administration of Kadian™ to patients with chronic cancer pain support the utility of this product in either a once daily or twice daily treatment regimen.

D. Dissolution Characteristics NDA Volume 26

1. *In-Vitro* Dissolution Data for Batches Used in Clinical Trials

When reduced to common combinations of capsule and pellet batches, including special batches, the clinical trials included in this submission utilized 22 capsules batches. The dissolution data for these 22 capsule batches are summarized in the following table.

Table 10: Summary of Kadian™ Capsule Dissolution Data

Capsule Batch	Strength (mg)	Pellet Batch	Capsule Batch Size	Percent Dissolved 1 Hr	2 Hr	4 Hr	6 Hr	8 Hr	9 Hr
D3835	100	D3832	43,420	-	6.7%	38.4%	73.5%	95.6%	-
D3836	50	D3832	101,300	-	4.6%	36.0%	71.0%	95.6%	-
D3837	20	D3832	144,800	-	1.0%	31.5%	70.5%	97.0%	-
D4632	10	D3832	2,040	-	7.0%	37.0%	71.0%	95.0%	-
D3838	100	D3830	38,800	-	6.7%	39.4%	74.3%	94.4%	-
D3839	50	D3830	90,600	-	5.0%	36.0%	70.0%	93.0%	-
D3840	20	D3830	129,691	-	5.5%	38.0%	73.5%	93.0%	-
D4700	100	D4698	186,930	-	8.3%	34.8%	66.3%	90.0%	-
D4701	50	D4698	720,300	-	21.8%	55.7%	87.7%	105.4%	-
D4702	20	D4698	155,720	-	6.0%	34.5%	69.0%	93.5%	-
3082001	20	3022001	162,960	0.0%	6.0%	35.0%	72.5%	94.5%	-
3085013	100	3022001	107,120	1.1%	8.0%	38.5%	74.4%	99.8%	-
3080008	50	3022002	108,350	0.2%	6.2%	34.8%	70.4%	94.8%	-
4070045 (a)	50	4101005	102,789	1.6%	8.8%	37.4%	72.6%	97.0%	-
PI-380 (b)	50	IB-015 & IB-013	192,440	1.8%	-	37.3%	73.3%	-	98.4%
4029008 (c)	50	4016001	4,183	2.4%	9.8%	41.0%	76.6%	98.0%	-
D4593 (d)	50	D4508	18,300	-	10.6%	60.6%	94.8%	99.4%	-
D4594 (e)	50	D4589	15,600	-	2.4%	16.0%	33.6%	53.4%	-
D7093 (d)	50	D7038	11,440	2.8%	12.0%	47.6%	83.2%	96.0%	-
D7089 (d)	50	D6923	15,600	1.4%	8.4%	44.4%	80.6%	99.6%	-
D7092 (e)	50	D6925	18,110	1.6%	7.4%	28.0%	56.8%	82.4%	-
D7134 (f)	50	D7122	16,400	0.2%	6.8%	37.2%	74.0%	99.2%	-

(a) Australian Commercial-scale Production Batch
(b) US Mid-scale Commercial Test Batch
(c) Australian Pilot-scale Batch
(d) special fast-dissolving batches
(e) special slow-dissolving batches
(f) special intermediate-dissolving batch

2. Proposed *In-Vitro* Dissolution Specifications

The following is a description of the proposed *in vitro* dissolution method as applied to product manufactured for the United States market.

Dosage Form: Kadian™ Capsules

Strengths: 20 mg, 50 mg, and 100 mg

Apparatus: USP 23, Apparatus I

Media: Sequential Dissolution Method. Acid Phase - 0.1N hydrochloric acid; Buffer Phase - phosphate buffer at pH 7.5. Dissolution is tested for one hour in acid followed by 8 hours in buffer.

Volume: 500 mL

Speed of Rotation: 100 rpm

Sampling Times: 1, 4, 6, and 9 hours

Analytical Method: HPLC Method LC/2054/DI

The proposed *in vitro* dissolution specification is summarized in the following table.

Table 11: Proposed *In Vitro* Dissolution Specifications

Time (hours)	Amount Released (%)
1	Not More Than 10%
4	28% - 45%
6	55% - 85%
9	Not Less Than 85%

Information on the relationship between *in vitro* dissolution and *in vivo* bioavailability can be found in the section on *in vitro* - *in vivo* correlation studies below (Section F).

000194

E. Pharmacokinetic-Pharmacodynamic Correlations NDA Volume 26

The relationship between the plasma concentrations of morphine and the pharmacodynamic effects of morphine was explored in three of the studies previously discussed in this summary. Study MOBU7/90-2 explored the pharmacokinetic-pharmacodynamic effects of morphine following administration of single doses of Kadian™ and an oral morphine solution under fasting conditions in healthy subjects. This study examined the relationship between morphine plasma concentrations and effect on sedation and nausea (by visual analogue scale), pupil diameter, respiratory rate, pulse, oxygen saturation, and end tidal CO_2.

Studies MOR-2/92 and MOR-9/92 also included the goal of examining pharmacokinetic-pharmacodynamic relationships under steady-state conditions in patients with cancer pain. Due to its early termination, study MOR-2/92 did not yield any meaningful data and will not be discussed. In study MOR-9/92, a compartment-independent modeling approach was used to correlate the plasma morphine and morphine plus morphine-6-glucuronide concentrations to pain scores measured on a visual analogue scale (VAS).

In study MOBU7/90-2, significant pharmacokinetic-pharmacodynamic relationships were observed for morphine-induced miosis and respiratory depression as measured by pupil diameter and end tidal CO_2 in this single-dose experiment (refer to Table 12). For both measures, significant physiological lag-times were observed for both onset and recovery. In addition, for both measures the mean E_{max} values (observed maximal effect) following administration of Kadian™ and the solution were nearly identical, in spite of a nearly two-fold difference in mean C_{max} values. Pupil diameter and end tidal CO_2 did change in line with *slow* increases in plasma morphine concentrations, but they did not track with *fast* increases, and they were slow to respond to decreases in plasma morphine concentrations. The results demonstrate that while these effect measures are clearly related to morphine plasma concentrations, they are of limited utility for detailed characterization of differences in morphine plasma concentrations.

Table 12: Summary of Mean (± S.D.) Pharmacokinetic and Pharmacodynamic Variables (Study MOBU7/90-2)

		Kadian™ 50 mg		Solution 25 mg		
Parameter	Variable	mean	S.D.	mean	S.D.	difference
Plasma Morphine Concentration (ng/mL)	AUC_{0-12} (ng•hr/mL)	53.89	25.33	44.15	11.85	9.74
	C_{max} (ng/mL)	8.12	3.85	15.89	6.52	-7.77
	T_{max} (hr)	7.77	1.81	0.96	0.34	6.81
VAS Sedation (mm)	$AUEC_{0-12}$ (mm•hr)	210.33	176.58	234.35	182.87	-24.02
	E_{max} (mm)	44.57	29.79	47.03	29.56	-2.46
	TE_{max} (hr)	5.59	3.26	4.30	2.96	1.31
VAS Nausea (mm)	$AUEC_{0-12}$ (mm•hr)	85.54	80.25	74.49	98.28	11.05
	E_{max} (mm)	20.43	19.02	13.40	14.27	7.03
	TE_{max} (hr)	5.81	3.99	4.00	3.60	1.79
Pupil Diameter (mm)	$AUEC_{0-12}$ (mm•hr)	43.91	6.83	42.62	5.30	1.28
	E_{max} (mm)	4.58	0.87	4.31	0.59	0.27
	TE_{max} (hr)	1.19	1.51	0.67	1.53	0.52
	E_{min} (mm)	3.18	0.51	3.18	0.46	0.00
	TE_{min} (hr)	5.73	3.45	2.92	2.36	2.81
Respiratory Rate (Respirations/min)	$AUEC_{0-12}$ (rpm•hr)	180.0	24.8	176.4	24.3	3.58
	E_{max} (rpm)	20.1	2.2	19.8	2.5	0.27
	TE_{max} (hr)	4.3	3.5	6.1	4.1	-1.84
	E_{min} (rpm)	10.8	2.5	10.4	2.3	0.40
	TE_{min} (hr)	5.1	4.1	5.0	3.1	0.12
Oxygen Saturation (%)	$AUEC_{0-12}$ (%•hr)	1150.8	11.9	1145.7	14.2	5.18
	E_{max} (%)	98.4	1.0	98.1	1.1	0.27
	TE_{max} (hr)	4.2	3.7	3.0	3.6	1.18
	E_{min} (%)	94.5	1.7	93.7	1.9	0.80
	TE_{min} (hr)	4.0	3.2	3.4	3.1	0.63
End Tidal CO_2 (%)	$AUEC_{0-12}$ (%•hr)	514.1	29.3	520.1	26.8	-5.91
	E_{max} (%)	48.9	4.4	48.3	2.7	0.60
	TE_{max} (hr)	6.3	3.8	4.6	3.6	1.69
	E_{min} (%)	36.3	4.0	36.7	4.4	-0.37
	TE_{min} (hr)	3.0	3.3	3.6	4.1	-0.62
Pulse Rate (Beats/min)	$AUEC_{0-12}$ (bpm•hr)	726.8	88.7	732.2	89.6	-5.42
	E_{max} (bpm)	74.0	8.1	73.7	7.8	0.33
	TE_{max} (hr)	5.7	4.6	6.5	4.6	-0.77
	E_{min} (bpm)	53.1	7.9	53.2	8.0	-0.17
	TE_{min} (hr)	5.3	3.7	4.8	3.5	0.49

$AUEC_{0-12}$ - area under the effect-time curve, 0-12 hr
E_{max} - observed maximal effect
TE_{max} - time of observed maximal effect
E_{min} - observed minimum effect
TE_{min} - time of observed minimum effect
rpm = respirations per minute; bpm = beats per minute

000196

In study MOR-9/92, the modeling results demonstrate a significant concentration-effect relationship for morphine and VAS pain scores that is independent of the formulation (Kadian™ administered once daily or MS Contin® administered twice daily). Since the patients were titrated to an individualized effective morphine dose, there was little fluctuation in pain scores during the observation period. Even though the design of the study made it difficult to obtain precise estimates of the effect parameter values, the results from the modeling clearly indicated that for most patients, pain relief was a function of the plasma morphine concentration.

The differential equation used to describe morphine concentrations over time at the effect site was

$$DZ(1) = K_{eo} * C_p - K_{eo} * Z(1)$$

where K_{eo} is a first-order transfer rate constant, C_p is the observed plasma morphine concentration, and Z(1) is the predicted morphine concentration at the effect site. This equation was fit simultaneously with the PD model equation using PCNONLIN, version 5.0 Alpha.

The PD model was

$$FR = CE^{\gamma}/(EC_{50}^{\gamma} + C_e^{\gamma})$$

Where FR is the fraction of the total response (calculated as (100 - VAS score)/100), C_e is the predicted morphine concentration at the effect site, EC_{50} is the plasma morphine concentration resulting in half-maximal response, and γ is a constant that determines the steepness of the concentration-effect response profile.

Patients who took rescue medication six hours or later following the morning dose were modeled up to the time of rescue; data from patients who took rescue medication within six hours following the morning dose were not used. In some cases, there was an insufficient amount of plasma morphine concentration-time data or VAS pain scores prior to rescue medication for PK/PD modeling to be meaningful. There were 14 patients who had acceptable data on both treatments. Results of these analyses are reported in the following table.

Table 13: Mean[1] Steady-State Pharmacokinetic-Pharmacodynamic Parameters for Kadian™ Administered Once Daily and MS Contin® Administered Twice Daily (Study MOR-9/92)

PK/PD Parameter	Kadian™ q 24 hr	MS Contin® q 12 hr
Number of Patients with Evaluable Data	14	14
Dose (mg)	96.43 ± 71.53	93.57 ± 74.07
EC_{50} (ng/mL)	0.2735 ± 0.5869	0.6845 ± 1.2400
K_{eo} (hr^{-1})	1.8937 ± 3.5155	1.2274 ± 2.8089
Gamma	0.6061 ± 0.4910	0.7937 ± 0.7100
Correlation	0.9939 ± 0.0090	0.9727 ± 0.0758

[1] Data are presented as the mean ± SD.

Adequate VAS data were available from the MS Contin® and Kadian™ treatment groups to provide acceptable PK/PD parameter estimates for both treatments for 14 of the patients. Although there is a great deal of variability among patients, mean values could be used to compare relative parameter estimates between the two treatments.

Because the maximum possible VAS score was 100 and the minimum possible score was 0, E_{max} was set at 100 for the fitting process so observed VAS scores would range from 0 to 100. Also, because good pain control was maintained for the duration of the study, pain scores were generally near 100 (maximum pain control). Nevertheless, there were difference's in some mean parameter values between the two treatments; dose was 96.3 and 93.6 mg, EC_{50} was 0.273 and 0.684 ng/mL, K_{eo} was 1.89 and 1.23 hr^{-1}, and gamma was 0.994 and 0.973 for Kadian™ and MS Contin®, respectively.

These mean values indicate that: 1) doses were only slightly greater for Kadian™ than for MS Contin®; 2) concentrations at which the effect is half-maximal (EC_{50} values) were less for Kadian™ than for MS Contin® which could mean that the lower fluctuation index achieves the same pain relief at a lesser morphine concentration; 3) the rate constant for transfer to the effect site (K_{eo}) was slightly

greater for Kadian™ ($T_{1/2}$ = 22 min) than for MS Contin® ($T_{1/2}$ = 34 min) implying that the onset of pain relief would be faster for Kadian™; and 4) gamma values were comparable and near unity which should be the case for a single fast acting narcotic analgesic agent, morphine.

F. In Vitro/In Vivo Correlation NDA Volume 26

Three single dose studies (MOBU-10/90, MOR-8/92, MOR-13/94) were conducted using a range of formulations, with varying *in vitro* dissolution profiles. In MOBU-10/90, slow, standard and fast release capsules were administered to 24 subjects as a three-way crossover study. In MOR-8/92, four formulations were tested in a cross-over study involving 16 subjects. The results from these first two studies were used to successfully establish Level A, Level B and Level C *in vitro/in vivo* correlations, as defined by the Food and Drug Administration. Subsequently, the Level A correlation was applied to study MOR-13/94, in which 34 subjects received three standard formulations (Australian pilot-scale batch, Australian commercial-scale batch and USA mid-scale commercial test batch).

Study MOBU-10/90 examined the biovailability and pharmacokinetics of three batches of Kadian™ Capsules exhibiting three widely varying dissolution profiles.

Table 14: Capsule Dissolution Results and Draft Specifications (Study MOBU-10/90)

	Amount Dissolved (mg)			
Time (hr)	HDR	MDR	LDR	Draft Specification for 50 mg Capsule[1]
2	5.3	2.3	1.2	Less than 8.0 mg
4	30.3 H	18.0	8.0 L	Between 12.5 and 26.5 mg
6	47.4 H	35.5	16.8 L	Between 27.0 and 41.5 mg
8	49.7	47.8	26.7 L	Not less than 37.5 mg

L = below specification; H = above specification
HDR = High dissolution rate
MDR = Medium dissolution rate
LDR = Low dissolution rate
[1] Draft dissolution specifications set at the time of manufacture of these batches (1991). Refer to Table 2.4 for current proposed specification.

The morphine pharmacokinetic parameters for the three batches are summarized in the following table:

Table 15: Mean[1] Morphine Pharmacokinetic Parameters Following Administration of Three Kadian™ Batches with Different Dissolution Rates (Study MOBU-10/90)

Parameter	HDR	MDR	LDR
C_{max} (ng/mL)	10.20*	7.88	6.11*
T_{max} (hr)	6.71	7.58	12.29*
AUC_{0-48}(ng•hr/mL)	137.64	139.99	136.83
$AUC_{0-\infty}$ (ng•hr/mL)	178.26*	194.06	189.20
λ_n (hr^{-1})	0.044	0.033	0.039
$T_{1/2}$ (hr)	19.44	23.56	20.60
WIDTH (hr)	4.07	6.00	12.37*
ln-C_{max} (ng/mL)	2.266*	2.007	1.756*
ln-AUC_{0-48} (ng•hr/mL)	4.879	4.898	4.875
ln- $AUC_{0-\infty}$ (ng•hr/mL)*	5.122*	5.227	5.191

[1] Least-square means
* Significant difference from MDR, $p < 0.05$
HDR = High dissolution rate
MDR = Medium dissolution rate
LDR = Low dissolution rate

All three batches were bioequivalent with respect to AUC_{0-48} (natural and ln-transformed values), indicating that changing the dissolution rate did not have any effect on the extent of morphine absorption. While the HDR batch had a significantly lower $AUC_{0-\infty}$ than the MDR batch, this difference represented only a difference in the area extrapolated beyond the last measured concentration (48 hours), owing to the differences in the observed elimination rate. Given the nearly identical results for AUC_{0-48} and the narrow confidence intervals (90% confidence interval, 93.8% to 102.8%), the difference in $AUC_{0-\infty}$ is highly unlikely to be due to a difference in the total extent of morphine absorption. Nevertheless, although the means were statistically different, the 90% confidence limit for the difference (86.2% to 97.5%) fell within the criteria for bioequivalence.

Study MOR-8/92 further explored the *in vivo* performance of batches of Kadian™ Capsules with differing dissolution profiles.

Table 16 provide the dissolution results for the few batches tested and Table 17 provides the mean morphine pharmacokinetic results for those batches.

000200

Table 16: Capsule Dissolution Results and Draft Specifications (Study MOR-8/92)

Time (hr)	Amount Dissolved (mg)				
	HDR 1	HDR 2	CDR	SDR	Draft Specification for 50 mg Capsule[1]
1	1.4	0.7	0.1	0.8	Not more than 5.0 mg (≤ 10%)
2	6.0	4.2	3.4	3.7	Not more than 10.0 mg (≤ 20%)
4	23.8	22.2	18.6	14.0 L	Between 16.2 and 24.8 mg (32.4 - 49.6%)
6	41.6	40.3	37.0	28.4 L	Between 31.2 and 45.3 mg (62.4 - 90.6%)
8	48.0	49.8	49.6	41.2 L	Not less than 42.3 mg (≥ 84.6%)

L = below specification; H = above specification
SDR = Slow dissolution rate (#D7092)
CDR = Central dissolution rate (#D7134)
HDR 1 = High dissolution rate 1 (#D7093)
HDR 2 = High dissolution rate 2 (#D7089)
[1] Draft specification set at the time of producing batches for this study (1992). Refer to Table 2.4 for current proposed specifications.

Both "faster dissolution" batches (HDR 1 and HDR 2) fell within the upper limits of the draft dissolution specifications, with the HDR 1 batch having a slightly faster dissolution rate than the HDR 2 batch. The "slower dissolution" batch (SDR) fell below the dissolution specifications at 4, 6, and 8 hours. In contrast to the batches tested in study MOBU-10/90, the dissolution rates at the high and low-ends for the batches tested in this trial were not as extreme. This was true even after consideration of the change in draft specifications between the two studies.

The morphine plasma concentration-time profiles indicated that the terminal concentrations were not declining, resulting in an inability to calculate a terminal elimination rate constant. As a result, λ_n, $T_{1/2}$, and $AUC_{0-\infty}$ were not calculated. The remaining pharmacokinetic parameters are summarized in the following table.

000201

Table 17: Mean[1] Morphine Pharmacokinetic Parameters Following Administration of Four Kadian™ Batches with Different Dissolution Rates (Study MOR-8/92)

Parameter	HDR 1	HDR 2	CDR	SDR
C_{max} (ng/mL)	10.479*	8.786	8.850	7.541
T_{max} (hr)	7.063	8.750	8.375	8.875
AUC_{0-36}(ng•hr/mL)	138.486	134.547	135.752	131.615
WIDTH (hr)	5.196	7.834*	5.270	8.014*
ln-C_{max} (ng/mL)	2.293*	2.089	2.138	1.946*
ln-AUC_{0-36} (ng•hr/mL)	4.896	4.858	4.878	4.839

[1] Least-square means
* Significant difference from CDR, $p < 0.05$
SDR = Slow dissolution rate (#D7092)
CDR = Central dissolution rate (#D7134)
HDR 1 = High dissolution rate 1 (#D7093)
HDR 2 = High dissolution rate 2 (#D7089)

This study demonstrated that changing the dissolution rate of Kadian™ capsules has no effect on the extent of morphine absorption; however, the fastest and slowest dissolving capsules included in the study were not bioequivalent to the capsule with a "central" dissolution rate (CDR) with respect to the rate of absorption (as measured by differences in C_{max}). The slowly dissolving capsule (SDR) Had dissolution rates that fell below the draft *in vitro* dissolution specifications and produced a lower and greater width than the CDR capsule. The HDR 1 capsule, while differing significantly from the CDR capsule, was also not bioequivalent to the HDR 2 capsule even though the two capsules had very similar *in vitro* dissoltuion profiles.

A Level A correlation, which is likely to exist when absorption of drug is rate limited by dissolution or release, was investigated using *in vitro* dissolution data and *in vivo* plasma morphine concentration versus time data for the three formulations tested in the MOBU-10/90 study. For each formulation, deconvolution of mean data was used to obtain the absorption versus time relationship. The results of the deconvolution procedure indicated that the rate of *in vivo* absorption was closely related to *in vitro* dissolution. A similar method was used to establish a Level A correlation for the products tested in the MOR-8/92 study.

The validity of the Level A correlation has subsequently been confirmed using *in vitro* dissolution data as an input function to model the plasma concentration versus time profiles. In this case, the *in vivo* dispositional functions, K_{el} (the elimination rate constant) and V/F (volume of distribution corrected for absolute availability), were estimated and the goodness of fit assessed by the correlation coefficient. The results of these analyses indicate that in all cases the dispositional parameters were similar and the quality of fit good ($r>0.9838$).

A Level B correlation utilises the principles of statistical moment analysis, whereby a dissolution parameter is compared to either the mean residence time (MRT) or the mean resident time for absorption (MRT_{abs}). For the slow, reference and fast release products tested in MOBU-10/90 study, the MRT_{abs} were 3.2, 4.5 and 10.2 hours, respectively. There was a clear rank order relationship between these *in vivo* parameters and the time to 50% dissolution (3.4, 4.6 and 7.7 hours, respectively), demonstrating a Level B correlation.

A Level C correlation relates *in vitro* dissolution data to a single pharmacokinetic parameter. In attempts to establish Level C correlations, the following parameters were choses ($AUC_{0\text{-}48h}$, C_{max}). Form the MOBU-10/90 results, highly significant Level C correlations ($p<0.001$) were established between C_{max} and various measures of *in vitro* dissolution, including percent dissolved at various times and dissolution rate constant. However, in keeping with the fact that all three formulations were equivalent in terms of $AUC_{0\text{-}48h}$, there was no correlation between *in vitro* dissolution parameters and extent of absorption. Similar results were obtained using data from the MOR-8/92 study.

Significant Level A, B and C relationships have been established between *in vitro* dissolution data and *in vivo* indices of rate of absorption. However, within the *in vitro* release limits of the formulation tested during product development (in MOBU-10/90, MOR-8/92 and MOR-13/94), there were no differences in extent of absorption, as assessed by AUC. These findings indicate that the dissolution process for Kadian™ is a good indicator of *in vivo* performance. Consequently, release and expiry limits for Kadian® can be based on the correlations established and changes in manufacturing can be evaluated using *in vitro* dissolution without the need for human testing.

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APPLICATION SUMMARY

7. CLINICAL DATA SUMMARY

A. Clinical Pharmacology **NDA Volume 59**

Throughout this NDA Faulding's morphine sulfate sustained-release capsules are designated as KADIAN™ (the proposed US trade name), KAPANOL® (the trade name used in other regions), MOLLY (its original project code name) and Morphine Sulfate Extended-Release Capsules (by Purepac Pharmaceutical Co., the US contract manufacturer).

Orally administered morphine is considered by many physicians to be the opioid drug of choice in the treatment of chronic pain, particularly cancer pain (Twycross and Lack, 1989; WHO, 1986). Although morphine is not a panacea for cancer pain, if properly used it is both effective and safe.

A major disadvantage of orally administered immediate-release morphine is the requirement for a dosing interval consistent with the terminal half-life of morphine, namely, three to four hours. The administration of larger morphine doses at longer time intervals will result in the development of tolerance but may also result in unacceptable side effects including sedation, nausea and vomiting, respiratory depression, or unacceptable periods of inadequate pain control. A solution to this problem would be an oral controlled-release formulation of morphine with a dosing interval of at least 12 hours, which should result in fewer medication errors, improved compliance, and possibly milder and less frequent morphine-related side effects.

A controlled-release product, MS Contin® (The Purdue Frederick Company, Norwalk, CT), has been approved by the United States Food and Drug Administration (FDA) for the treatment of moderate to severe chronic pain. However, the pharmacokinetic profile of MS Contin® does not suggest a smooth sustained-release of the morphine dose over the desired 12-hour dosing interval. In addition, clinical experience with MS Contin® has shown a significant number of patients require more frequent dosing, e.g., every eight hours. In accordance with this experience, the product information for MS Contin® (Physicians' Desk Reference, 1995, page 1933) recommends administration every eight or twelve hours.

Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same for immediate or sustained-release formulations, although the time to peak blood level (T_{max}) will be longer and the maximum concentration (C_{max}) will be lower for formulations that effectively reduce the rate of release of morphine to the gastrointestinal tract. This slower rate of release may result in the perception of under-dosing until steady-state blood levels are achieved, particularly in patients requiring higher total daily doses of morphine (daily need greater than 120 mg/day), Such patients are sensitive to withdrawal and under-dosing when converting from an immediate-release product such as morphine solution to a sustained-release product such as Kadian™ even though the total daily dose is the same for both preparations.

Because of pre-systemic elimination only about 20 - 40% of the administered dose of morphine reaches the central compartment. Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain. Morphine also crosses the placental membranes and has been found in breast milk. Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites including morphine-3- and morphine-6-glucuronide. The glucuronide system has a very high capacity and is not easily saturated even in disease. Morphine has a reported oral bioavailability of 20 - 40%, a volume of distribution (V_d) of 2 - 4 liters/kg, a clearance of 0.9 - 1.2 liters/kg/hr, and a terminal elimination half-life of 2 to 4 hours. Following the administration of oral morphine solution, approximately fifty percent of the morphine that will ever reach the central compartment intact, reaches it within 30 minutes.

KADIAN™ Morphine Sulfate Sustained-release Capsules 20 mg, 50 mg, and 100 mg have been developed by F. H. Faulding & Co. Limited, an Australian pharmaceutical company, based in Salisbury in South Australia. (Faulding Inc., the sponsor of this NDA is a US based wholly owned subsidiary of Faulding.)

The technology applied to KADIAN™ is similar to that applied by Faulding in the development and manufacture of its other modified release products approved in the US, including Eryc® (erythromycin - enteric), Doryx® (doxycycline - delayed-release) and Austyn® (theophylline - extended-release).

In summary, the modified release technologies developed by Faulding encompass production of a drug-containing CORE. The modified-release characteristics are provided by spray-coating the CORE in a fluid bed with an appropriate combination of polymers to produce the PELLET. The appropriate polymers are selected to provide the combination which, when applied to the CORE, produces the required drug release profile *in vitro* and *in vivo*. Polymers are generally selected from groups which are generally recognized as safe and in use in other pharmaceutical products, are of an appropriate grade or standard and have the required properties of hydrophobicity, hydrophilicity or varying solubilities at different pH's. Drug release characteristics of a formulation are controlled by the appropriate combination of polymers and the application of the correct weight or thickness of coat.

Finally, the modified-release PELLETS are encapsulated into hard gelatin capsules to produce the finished product dosage form. Generally, Faulding modified-release products rely on formulating one single PELLET or two blended PELLETS to produce all dosage strengths of a particular product. Thus the only difference between dosage strengths is the size of the capsule and quantity of PELLETS filled into that capsule.

Table 1: Table of Clinical Pharmacology Studies

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects Treated	Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs (vol/page) 4) IND Serial No.
MOBU7/90-2 United States M. Allen Tompkins, MD	Completed Dec. 7, 1990 - Dec. 24, 1990	Single-dose, 3-way crossover study in normal volunteers	Kadian™ 50 mg [fasted] Kadian™ 50 mg [fed] Morphine Solution 25 mg [fasted]	Randomized: 30 Completed: 30	23.8 ± 5.4 30 M, 0 F 29 W, 1 NW	1) 034 / 001 2) 137 / 067 3) — 4) 037
MOB-1/90 Australia Dr. David A Cherry	Completed April 4, 1991 - July 2, 1992	Multiple-dose, randomized, open-label, three-way crossover study in cancer patients.	Kadian™ q12h (x 7 days) MST Continus® q12h (x 4-7 days) Morphine Solution q4h (x 4-7 days)	Randomized: 34 Completed: 24	64.6 ± 10.7 36 M, 14 F 50 W, 0 NW	1) 027 / 001 2) 137 / 001 3) 150 / 131 4) 064
KAP-RRC/91/01 United States M. Allen Tompkins, MD	Completed April 19, 1991 - May 6, 1991	Single-dose, 3-way crossover study in normal volunteers	Kadian™ 50 mg MST Continus® 60 mg Morphine Solution 25 mg	Randomized: 27 Completed: 24	30.0 ± 7.4 27 M, 0 F 25 W, 2 NW	1) 041 / 001 2) 137 / 001 3) 150 / 061 4) 058
MOBU-9/90 United States M. Allen Tompkins, MD	Completed April 26, 1991 - May 20, 1991	Single-dose, randomized, open-label, four-way crossover study in normal volunteers	Kadian™ 30 mg Kadian™ 50 mg Kadian™ 70 mg Kadian™ 100 mg	Randomized: 28 Completed: 24	26.8 ± 7.0 28 M, 0 F 21 W, 7 NW	1) 056 / 001 2) 137 / 130 3) — 4) 072

902000

Table of Clinical Pharmacology Studies (continued)

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects Treated	Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs (vol/page) 4) IND Serial No.
MOBU-10/90 United States M. Allen Tompkins, MD	Completed May 10 1991 - May 27, 1991	Single-dose, randomized, open-label, three-way crossover comparison of 3 lots with differing dissolution rates in normal volunteers	Kadian™ 50 mg (faster dissolution) Kadian™ 50 mg (central dissolution) Kadian™ 50 mg (slower dissolution)	Randomized: 24 Completed: 24	27.0 ± 7.5 24 M, 0 F 24 W, 0 NW	1) 050 / 001 2) 137 / 197 3) — 4) 068
083-031 United States Merlin Kampfer, MD	Completed Feb. 29, 1992 - March 14, 1992	Single-dose, randomized, two-way crossover study to validate method of blinding for Phase II/III clinical trials. Conducted in normal volunteers	MS Contin® Tablet 60 mg MS Contin ® Tablet 60 mg in a titanium dioxide capsule	Randomized: 16 Completed: 11 Evaluable: 10	28.8 ± 7.8 16 M, 0 F 16 W, 0 NW	1) 047 / 001 2) 137 / 300 3) 150 / 001 4) 082
MOR-8/92 United States James C. Kisicki, MD	Completed Nov. 20, 1992 - Dec. 20, 1992	Single-dose, randomized, four-way crossover comparison of 4 batches with differing dissolution rates. Conducted in normal volunteers	Kadian™ 50 mg (faster batch 1) Kadian™ 50 mg (faster batch 2) Kadian™ 50 mg (slower dissolution) Kadian™ 50 mg (central dissolution)	Randomized: 16 Completed: 16	26.8 ± 8.0 16 M, 0 F 15 W, 1 NW	1) 053 / 001 2) 137 / 240 3) — 4) 069

002007

Table of Clinical Pharmacology Studies (continued)

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects Treated	Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs (ol/page) 4) IND Serial No.
MOR-2/92 United States R.K. Portenoy, MD K. M. Foley	Study terminated prior to completion due to poor recruitment & control of procedures. January 29, 1993 - December 19, 1993	Multiple-dose, randomized, double-blind, double-dummy, balanced incomplete block crossover design in cancer patients with moderate to severe pain.	Two of Three: Kadian™ q24h (x 4-7 days) Kadian™ q12h (x 4-7 days) MS Contin® q12h (x 4-7 days)	Randomized: 19 Completed: 16 Evaluable: 6	47.5 (23 - 71) 7 M, 12 F 17 W, 2 NW	1) 076 / 001 2) 147 / 174 3) 157 / 001 4) 087
MOR-13/94 Australia Dr. Alan F. Broomhead	Completed Nov. 30, 1994 - Dec. 16, 1994	Single-dose, 3-way crossover study in normal volunteers	Kadian™ 50 mg: Australia Commercial-scale batch Australia Pilot-scale batch US Commercial Test-scale batch	Randomized: 36 Completed: 34	22.4 ± 4.4 36 M, 0 F 35 W, 1 NW	1) 044 / 001 2) 137 / 267 3) — 4) 089
MOR-9/92 Australia Dr. David A. Cherry	Completed, July 15, 1993 - Dec. 30, 1994	Multiple-dose, randomized, double-blind, double-dummy, two-way crossover in cancer patients with moderate to severe chronic pain	Kadian™ q24h (x 7 ± 1 days) MS Contin® q12h (x 7 ± 1 days)	Randomized: 29 Completed: 25 Evaluable: 24	64.9 ± 13.2 18 M, 11 F 29 W, 0 NW	1) 077 / 001 2) 140 / 001 3) 155 / 192 4) 092

002208

1. Single Dose Pharmacokinetic Studies in Healthy Subjects

   a. Introduction and Overview

   Seven (7) single-dose randomized, crossover studies were conducted in healthy subjects. These studies included investigations of: the bioavailability of Kadian™ with respect to an immediate-release oral solution and an approved controlled-release product (MST Continus®/MS Contin®); the effect of food on Kadian™ bioavailability; pharmacokinetic linearity and dose-proportionality after increasing Kadian™ doses; *in vitro/in vivo* correlations; the bioequivalence of Kadian™ batches manufactured at different scales and at different sites (Australia and USA); and the effect on bioavailability of placing an MS Contin® tablet inside an opaque capsule. The results of the seven single-dose trials are summarized in the following table:

Table 2: Summary of Mean[1] Single-Dose Pharmacokinetic Data

Study	Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng·hr/mL)	WIDTH (hr)
MOBU7/90-2	Kadian™ 50mg (fasted) [2]	4.06	8.47	63.38 [a]	**6.70**
	Kadian™ 50mg (fed) [2]	3.61	10.13	65.67 [a]	**8.27**
	Solution 25mg (fasted)[2]	15.89	0.96	59.37 [a]	**0.94**
KAP-RRC/91/01	Kadian™ 50mg [2]	3.90	8.58	67.75 [a]	**6.29**
	MST Continus® 60mg[2]	7.63	2.46	76.07 [a]	**2.46**
	Solution 25mg[2]	16.11	0.88	90.69 [a]	**1.17**
MOR-13/94	Kadian™ 50mg [A]	11.10	7.57	137.42 [b]	**3.98**
	Kadian™ 50mg [B]	10.19	7.80	137.27 [b]	**4.97**
	Kadian™ 50mg [C]	10.61	8.10	134.38 [b]	**4.67**
MOBU-10/90	Kadian™ 50mg (LDR)	6.11	12.29	136.83[a]	**12.37**
	Kadian™ 50mg (MDR)	7.88	7.58	139.99 [a]	**6.00**
	Kadian™ 50mg (HDR)	10.20	6.71	137.64 [a]	**4.07**
MOR-8/92	Kadian™ 50mg (HDR 1)	10.48	7.06	138.49 [b]	**5.20**
	Kadian™ 50mg (HDR 2)	8.79	8.75	134.55 [b]	**7.83**
	Kadian™ 50mg (CDR)	8.85	8.38	135.75 [b]	**5.27**
	Kadian™ 50mg (SDR)	7.54	8.88	131.62 [b]	**8.01**
MOBU-9/90	Kadian™ 30mg	4.55[3]	7.79	81.75 [a,3]	**7.33**
	Kadian™ 50mg	7.81[3]	7.21	136.33 [a,3]	**6.32**
	Kadian™ 70mg	12.69[3]	8.42	196.99 [a,3]	**5.66**
	Kadian™ 100mg	17.78[3]	8.42	273.65 [a,3]	**5.01**
083-031	MS Contin® 60mg (TiO_2)	15.56	2.42	131.64	-
	MS Contin® 60mg	14.49	2.35	139.50	-

[a] AUC_{0-48}
[b] AUC_{0-36}
[1] Least-square means
[2] C_{max} & AUC_{0-t} adjusted to 25 mg dose
[3] Arithmetic means
LDR - low dissolution rate
MDR - medium/central dissolution rate
HDR - high dissolution rate
[A] Australian Pilot-Scale Batch
[B] Australian Commercial-Scale Batch
[C] US Mid-Scale Commercial Test Batch
HDR 1 - high dissolution rate 1
HDR 2 - high dissolution rate 2
CDR - central dissolution rate
SDR - slow dissolution rate
(TiO_2) - encapsulated in an opaque white (TiO_2) capsule

The plasma concentrations and concentration-derived parameters (e.g., AUC_{0-t} and C_{max}) were adjusted to a 25 mg dose in the two single-dose studies that included an immediate-release solution (MOBU7/90-2 and KAP-RRC/91/01).

000210

While it is generally considered appropriate to compare $AUC_{0-\infty}$ values between treatments in single-dose studies, the majority of bioequivalence/bioavailability comparisons were made on the basis of AUC_{0-t} values due to the fact that half-life could not be determined for a number of subjects. Within the individual studies, it was apparent that any observed differences between $AUC_{0-\infty}$ values were a reflection of differences in estimates of the extrapolated area due to differences in the estimates of the terminal elimination rate constant. Examination of the AUC_{0-t} values across the studies that had different durations of sample collection would appear to further validate this conclusion. There are no apparent differences in the observed mean AUC_{0-t} values between study MOBU-10/90 (which measured AUC_{0-48}) and studies MOR-13/94 or MOR-8/92 (which measured AUC_{0-36}). Since the additional 12 hours of sample collection (from 36 to 48 hours) did not appear to add any appreciable area, it seems reasonable to conclude that absorption is complete by 36 hours and that comparison of the measured AUC through 36 or 48 hours is a true reflection of the extent of morphine delivery and absorption.

b. Summary and Conclusions

The six single-dose studies conducted with Kadian™, and the seventh study of encapsulated MS Contin® address a number of different issues, including:

- the single-dose bioavailability of Kadian™ relative to an immediate-release oral solution;
- the single-dose bioavailability of Kadian™ relative to a marketed, controlled-release product;
- the effect of the morphine delivery rate from Kadian™ on the metabolic profile of morphine;
- the effect of food on the bioavailability of morphine from Kadian™;
- the linearity of morphine pharmacokinetics following administration of increasing Kadian™ doses;
- the effect of different batch sizes and manufacturing sites on the performance of Kadian™;
- the effect of different dissolution rates on the performance of Kadian™; and
- the effect of encapsulating an MS Contin® tablet on the bioavailability of morphine.

The findings of these trials are summarized in the following paragraphs.

i. Single-dose bioavailability of Kadian™ relative to an immediate-release oral solution.

Studies MOBU7/90-2 and KAP-RRC/91/01 examined the bioavailability of morphine following administration of Kadian™ relative to an immediate-release oral solution, the most bioavailable reference form of oral morphine. These studies clearly demonstrated that the extent of morphine absorption following administration of Kadian™ is equivalent to the extent of morphine absorption following administration of an oral solution. In comparison with the most bioavailable oral formulation of morphine, the results demonstrate that the sustained-release technology employed in the Kadian™ formulation has no adverse impact on morphine bioavailability.

ii. Single-dose bioavailability of Kadian™ relative to a marketed, controlled-release product.

Study KAP-RRC/91/01 examined the bioavailability of morphine following administration of Kadian™ relative to a marketed, controlled-release formulation (MST Continus® Tablets, known as MS Contin® in the US). While the two products are not significantly different with respect to the extent of morphine absorption, there are substantial differences between the sustained-release characteristics of Kadian™ and MST Continus® (known as MS Contin® in the US). Following administration of Kadian™ the plasma morphine C_{max} is approximately 50% lower than that produced by MST Continus® and the T_{max} is approximately 3.5-fold longer.

iii. Effect of the morphine delivery rate from Kadian™ on the metabolic profile of morphine.

The molar plasma concentration ratios of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) were evaluated in subgroups of subjects in study MOBU7/90-2. Following administration of a single-dose to healthy volunteers, the molar ratios of morphine:M3G:M6G were 1:33:8, 1:29:7 and 1:27:7 for Kadian™ under fasting and fed conditions, and the immediate-release solution under fasting conditions, respectively. There were no statistically significant differences between the metabolite AUC values or ratios following administration of Kadian™ or the immediate-release solution. These data demonstrate that slowing the delivery rate for morphine with the Kadian™ formulation does not alter the metabolism of orally administered morphine under fed or fasting conditions.

iv. Effect of food on the bioavailability of morphine from Kadian™.

The bioavailability of morphine is unaffected by administration of Kadian™ in conjunction with a high-fat meal (Study MOBU7/90-2). The mean ratios (fed : fasted) and 90% confidence intervals for ln-transformed values of C_{max}, AUC_{0-48}, and $AUC_{0-\infty}$ were 94.0% (83.4%-106.0%), 104.2% (97.7%-111.2%), and 99.5% (92.0%-107.6%), respectively. All fell within the acceptance criteria for bioequivalence. There is no evidence that administration of Kadian™ with a high-fat meal resulted in dose-dumping or any loss of the sustained-release characteristics of the formulation.

v. Linearity of morphine pharmacokinetics following increasing doses of Kadian™.

The results of study MOBU-9/90 demonstrated that the pharmacokinetics of morphine are linear and dose-proportional following administration of single Kadian™ doses across the range from 30 to 100 mg. There are no significant differences in the terminal elimination rate, or in the dose-adjusted values for C_{max}, T_{max}, or AUC.

vi. Effect of different batch sizes and manufacturing sites on the performance of Kadian™.

The results of study MOR-13/94 showed that three different batches of Kadian™, a pilot-scale batch produced in Australia, a commercial-scale batch produced in Australia, and a mid-scale commercial test batch produced in the United States, are bioequivalent. In direct pair-wise comparisons (US mid-scale vs. Australian commercial-scale, Australian pilot-scale vs. Australian commercial-scale, and US mid-scale vs. Australian pilot-scale), the 90% confidence intervals for ln-transformed values of C_{min}, AUC_{0-36}, and $AUC_{0-\infty}$ were all well within the criteria for acceptance of bioequivalence. This study confirmed that different scale batches, produced in different plants, are bioequivalent *in vivo* when manufactured to meet the *in vitro* dissolution specifications proposed in this application. The results also confirmed the successful scale-up of production from pilot-scale to commercial-scale production batches. Considering these results, it is reasonable to conclude that product manufactured in the United States would be expected to match the *in vivo* performance of the product tested in clinical trials when held to the proposed dissolution specifications.

vii. Effect of altering in vitro dissolution rates on the in vivo bioavailability of Kadian™.

Studies MOBU-10/90 and MOR-8/92 compared the *in vivo* bioavailability of Kadian™ batches with different *in vitro* dissolution rates. The results demonstrated a general association between alteration of the *in vitro* dissolution rate and the observed C_{max} values. There was no effect of slower or faster *in vitro* dissolution rates on the extent of morphine absorption. Batches with slower dissolution rates produced lower C_{max} values and batches with higher dissolution rates produce higher C_{max} values. A detailed analysis of *in vitro-in vivo* correlations has been conducted and is summarized in the section on Human Pharmacokinetics and Bioavailability of this application.

viii. Effect of encapsulating an MS Contin® tablet on the bioavailability of morphine.

The results of Study 083-031 demonstrated that placing an MS Contin® tablet inside an opaque white capsule ("titanium dioxide capsule") did not have any adverse effect on the rate or extent of morphine bioavailability. The 90% confidence intervals for AUC_{0-36} and $AUC_{0-\infty}$ fell well within the criteria for bioequivalence. While the upper 90% confidence intervals for C_{max} slightly exceed the criteria for bioequivalence (122.8%), this was probably a reflection of the small sample size (n = 11) rather than a true difference. Even if the difference was real, the magnitude was trivial (an average increase in C_{max} of 1 ng/mL, 15.6 vs. 14.5 ng/mL), and not expected to influence the performance of MS Contin® when utilized in Phase II/III clinical studies.

2. Steady-State Pharmacokinetic Studies in Patients

a. Introduction and Overview

Three (3) multiple-dose, steady-state, randomized, crossover studies were conducted in patients with chronic cancer pain. These studies included investigations of steady-state morphine pharmacokinetics: following administration of Kadian™ every 12 hours in comparison to every 12 hour administration of MS Contin® tablets and every 4 hour administration of an immediate-release solution; following administration of Kadian™ every 12 or 24 hours in comparison to MS Contin® tablets administered every 12 hours; and following administration of Kadian™ every 24 hours in comparison to administration of MS Contin® tablets every 12 hours. One of the studies (MOR-2/92) was terminated early due to slow enrollment of patients and poor protocol compliance. As a result, meaningful pharmacokinetic data are available from two of the studies (MOB-1/90 and MOR-9/92). The results obtained from these studies are summarized in the following table.

b. Results and Conclusions

Table 3: Summary of Mean[1] Dose-Adjusted[2] Multiple-Dose Pharmacokinetic Data

Study	Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{ss} (ng·hr/mL)	C_{min} (ng/mL)	FLUCT 1	FLUCT 2	WIDTH (hr)
MOB-1/90	Kadian™ q12h	32.1	5.7	297.66	17.7	0.9	0.6	9.1
	MST Continus® q12h	42.3	3.4	272.42	9.2	4.3	1.5	3.1
	Solution	48.3	0.7	267.58	12.4	3.7	1.7	-
MOR-9/92	Kadian™ q24h	37.3	10.3	500.89	9.9	3.0	1.4	6.0
	MS Contin® q12h	36.9	4.4	457.28 [a]	7.6	4.1	1.6	4.8

[1] Least-square means
[2] concentrations and concentration-derived parameters adjusted to a dosage of 100mg per day.
[a] AUC_{0-24}

The results of study MOB-1/90 demonstrated that Kadian™ capsules exhibit a distinctly different concentration profile compared to both the solution and MS Contin® tablets. Kadian™ capsules produce a lower C_{max} value, a longer T_{max}, a higher C_{min}, and lower fluctuation indices than either the solution or MS Contin® tablets. By direct comparison, both Kadian™ and MS Contin® are bioequivalent to the solution and each other, only with respect to the extent of absorption (as measured by the AUC_{ss}). Beyond that, there are few similarities between Kadian™ and MS Contin®. In fact, the MS Contin® tablet is quite similar to the solution, with the exceptions that the MS Contin® tablet has significantly lower C_{min} and C_{max} values. In contrast, Kadian™ is characterized by significantly lower C_{max} values, higher C_{min} values, and lower fluctuation indices than either of the other two products; indicating that Kadian™ produces a more constant morphine plasma level and lower peak-to-trough fluctuation. There are also no significant differences between the three products with respect to the molar AUC ratios for morphine, morphine-3-glucuronide, and morphine-6-glucuronide.

The results of study MOR-9/92 revealed that Kadian™ administered once daily delivers an equivalent amount of morphine to MS Contin® tablets administered twice daily. The C_{max} value following administration of Kadian™ once daily is equivalent to the C_{max} following administration of MS Contin® twice daily even though the Kadian™ dose is twice the 12-hourly MS Contin® dose. The reduced peak-to-trough fluctuation in morphine plasma concentrations following Kadian™ administration is further characterized by lower fluctuation indices and higher C_{min} values.

In addition, once daily Kadian™ administration is associated with a longer T_{max} and plasma morphine concentrations were maintained at or above 75% of the C_{max} (WIDTH) for a longer period of time than is observed after twice daily administration of MS Contin®. There are no significant differences with respect to the molar AUC ratios for morphine, morphine-3-glucuronide, and morphine-6-glucuronide between Kadian™ administered once daily and MS Contin® administered twice daily.

Overall, the results of the multiple-dose, steady-state studies in patients demonstrate the following:

1) The extent of morphine absorption following administration of Kadian™ every 12 hours is equivalent to the extent of morphine absorption following administration of an oral solution every four hours. In comparison with the most bioavailable oral formulation of morphine, the results demonstrate that the sustained-release technology employed in the Kadian™ formulation has no adverse impact on morphine bioavailability. The results of these studies further illustrate the enhanced sustained-release profile of the product. In comparison to the immediate-release solution, Kadian™ clearly demonstrates sustained-release characteristics, including significantly lower C_{max} values, longer T_{max} values, higher C_{min} values, and lower fluctuation indices.

2) Administration of Kadian™ every 12 hours is equivalent to administration of MST Continus® every 12 hours with respect to the extent of morphine absorption; however, Kadian™ has a more enhanced sustained-release profile than MST Continus® as evidenced by significantly lower C_{max} values, longer T_{max} values, higher C_{min} values, and lower fluctuation indices.

3) Administration of Kadian™ once every 24 hours is equivalent to administration of MS Contin® every 12 hours with respect to the extent of morphine absorption; however, Kadian™ has a more enhanced sustained-release profile than MS Contin® as evidenced by significantly longer T_{max} values, higher C_{min} values, and lower fluctuation indices.

4) Slowing the rate of morphine delivery with Kadian™ does not alter the metabolism of morphine in patients.

5) The plasma morphine pharmacokinetic profiles following administration of Kadian™ to patients with chronic cancer pain support the utility of this product in either a once daily or twice daily treatment regimen.

3. Pharmacokinetic-Pharmacodynamic Correlations

a. Introduction and Overview

The relationship between the plasma concentrations of morphine and the pharmacodynamic effects of morphine was explored in three of the studies previously discussed in this summary. Study MOBU7/90-2 explored the pharmacokinetic-pharmacodynamic effects of morphine following administration of single doses of Kadian™ and an oral morphine solution under fasting conditions in healthy subjects. This study examined the relationship between morphine plasma concentrations and effect on sedation and nausea (by visual analogue scale), pupil diameter, respiratory rate, pulse, oxygen saturation, and end tidal CO_2.

Studies MOR-2/92 and MOR-9/92 also included the goal of examining pharmacokinetic-pharmacodynamic relationships under steady-state conditions in patients with cancer pain. Due to its early termination, study MOR-2/92 did not yield any meaningful data and will not be discussed. In study MOR-9/92, a compartment-independent modeling approach was used to correlate the plasma morphine and morphine plus morphine-6-glucuronide concentrations to pain scores measured on a visual analogue scale (VAS).

b. Results and Conclusions

In study MOBU7/90-2, significant pharmacokinetic-pharmacodynamic relationships were observed for morphine-induced miosis and respiratory depression as measured by pupil diameter and end tidal CO_2 in this single-dose experiment. For both measures, significant physiological lag-times were observed for both onset and recovery. In addition, for both measures the mean E_{max} values (observed maximal effect) following administration of Kadian™ and the solution were nearly identical, in spite of a nearly two-fold difference in mean C_{max} values. Pupil diameter and end tidal CO_2 did change in line with *slow* increases in plasma morphine concentrations, but they did not track with *fast* increases, and they were slow to respond to decreases in plasma morphine concentrations. The results, Table 4, demonstrated that while these effect measures are clearly related to morphine plasma concentrations, they are of limited utility for detailed characterization of differences in morphine plasma concentrations.

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Table 4: Summary of Mean (± S.D.) Pharmacokinetic and Pharmacodynamic Variables (Study MOBU7/90-2)

Parameter	Variable	Kadian™ 50 mg mean	Kadian™ 50 mg S.D.	Solution 25 mg mean	Solution 25 mg S.D.	difference
Plasma Morphine Concentration (ng/mL)	AUC_{0-12} (ng•hr/mL)	53.89	25.33	44.15	11.85	9.74
	C_{max} (ng/mL)	8.12	3.85	15.89	6.52	-7.77
	T_{max} (hr)	7.77	1.81	0.96	0.34	6.81
VAS Sedation (mm)	$AUEC_{0-12}$ (mm•hr)	210.33	176.58	234.35	182.87	-24.02
	E_{max} (mm)	44.57	29.79	47.03	29.56	-2.46
	TE_{max} (hr)	5.59	3.26	4.30	2.96	1.31
VAS Nausea (mm)	$AUEC_{0-12}$ (mm•hr)	85.54	80.25	74.49	98.28	11.05
	E_{max} (mm)	20.43	19.02	13.40	14.27	7.03
	TE_{max} (hr)	5.81	3.99	4.00	3.60	1.79
Pupil Diameter (mm)	$AUEC_{0-12}$ (mm•hr)	43.91	6.83	42.62	5.30	1.28
	E_{max} (mm)	4.58	0.87	4.31	0.59	0.27
	TE_{max} (hr)	1.19	1.51	0.67	1.53	0.52
	E_{min} (mm)	3.18	0.51	3.18	0.46	0.00
	TE_{min} (hr)	5.73	3.45	2.92	2.36	2.81
Respiratory Rate (Respirations/min)	$AUEC_{0-12}$ (rpm•hr)	180.0	24.8	176.4	24.3	3.58
	E_{max} (rpm)	20.1	2.2	19.8	2.5	0.27
	TE_{max} (hr)	4.3	3.5	6.1	4.1	-1.84
	E_{min} (rpm)	10.8	2.5	10.4	2.3	0.40
	TE_{min} (hr)	5.1	4.1	5.0	3.1	0.12
Oxygen Saturation (%)	$AUEC_{0-12}$ (%•hr)	1150.8	11.9	1145.7	14.2	5.18
	E_{max} (%)	98.4	1.0	98.1	1.1	0.27
	TE_{max} (hr)	4.2	3.7	3.0	3.6	1.18
	E_{min} (%)	94.5	1.7	93.7	1.9	0.80
	TE_{min} (hr)	4.0	3.2	3.4	3.1	0.63
End Tidal CO_2 (%)	$AUEC_{0-12}$ (%•hr)	514.1	29.3	520.1	26.8	-5.91
	E_{max} (%)	48.9	4.4	48.3	2.7	0.60
	TE_{max} (hr)	6.3	3.8	4.6	3.6	1.69
	E_{min} (%)	36.3	4.0	36.7	4.4	-0.37
	TE_{min} (hr)	3.0	3.3	3.6	4.1	-0.62
Pulse Rate (Beats/min)	$AUEC_{0-12}$ (bpm•hr)	726.8	88.7	732.2	89.6	-5.42
	E_{max} (bpm)	74.0	8.1	73.7	7.8	0.33
	TE_{max} (hr)	5.7	4.6	6.5	4.6	-0.77
	E_{min} (bpm)	53.1	7.9	53.2	8.0	-0.17
	TE_{min} (hr)	5.3	3.7	4.8	3.5	0.49

$AUEC_{0-12}$ - area under the effect-time curve, 0-12 hr
E_{max} - observed maximal effect
TE_{max} - time of observed maximal effect
E_{min} - observed minimum effect
TE_{min} - time of observed minimum effect
rpm = respirations per minute; bpm = beats per minute

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In study MOR-9/92, the modeling results demonstrate a significant concentration-effect relationship for morphine and VAS pain scores that is independent of the formulation (Kadian™ administered once daily or MS Contin® administered twice daily). Since the patients were titrated to an individualized effective morphine dose, there was little fluctuation in pain scores during the observation period. Even though the design of the study made it difficult to obtain precise estimates of the effect parameter values, the results from the modeling clearly indicated that for most patients, pain relief was a function the plasma morphine concentration.

In analysing the results of this study, the differential equation used to describe morphine concentrations over time at the effect site was

$$DZ(1) = K_{eo} * C_p - K_{eo} * Z(1)$$

where K_{eo} is a first-order transfer rate constant, C_p is the observed plasma morphine concentration, and Z(1) is the predicted morphine concentration at the effect site. This equation was fit simultaneously with the PD model equation using PC NONLIN, version 5.0 Alpha.

The PD model was

$$FR = CE^{\Upsilon}/(EC_{50}^{\Upsilon} + C_e^{\Upsilon})$$

Where FR is the fraction of the total response (calculated as (100 - VAS score)/100), C_e is the predicted morphine concentration at the effect site, EC_{50} is the plasma morphine concentration resulting in half-maximal response, and Υ is a constant that determines the steepness of the concentration-effect response profile.

Table 5: Mean[1] Steady-State Pharmacokinetic-Pharmacodynamic Parameters for Kadian™ Administered Once Daily and MS Contin® Administered Twice Daily (Study MOR-9/92)

PK/PD Parameter	Kadian™ q 24 hr	MS Contin® q 12 hr
Number of Patients with Evaluable Data	14	14
Dose (mg)	96.43 ± 71.53	93.57 ± 74.07
EC_{50} (ng/mL)	0.2735 ± 0.5869	0.6845 ± 1.2400
K_{eo} (hr^{-1})	1.8937 ± 3.5155	1.2274 ± 2.8089
Gamma	0.6061 ± 0.4910	0.7937 ± 0.7100
Correlation	0.9939 ± 0.0090	0.9727 ± 0.0758

[1] Data are presented as the mean ± SD.

4. Pharmacodynamic Dose-Range and Dose-Response

The purpose of this application is to verify the performance of an oral sustained-release delivery system for morphine (Kadian™ capsules). This was accomplished by conducting a series of pharmacokinetic studies in healthy subjects and patients, and clinical trials assessing analgesic effect in patients with cancer pain. The design of the clinical trials in patients with chronic cancer pain involved enrollment of patients who were already chronically receiving morphine for the treatment of pain, titrating the patients to a stable morphine regimen during a lead-in period, and then randomizing the patients who met the study requirements into the randomized, crossover or parallel portion of the trial. By design, no attempt was made in any of these trials to establish a dose-response relationship for the analgesic effect of morphine. The investigators were allowed to individualize the dosage of morphine for each study participant.

As a result of these design considerations, no attempt was made to examine or analyze the relationship between the dose of morphine and its analgesic effect. Placing morphine-dependent cancer patients on a pre-selected, fixed dose of morphine, as would be required by a dose-response design, was not deemed appropriate due to the potential for overdosage or underdosage, and the associated risks of unwarranted side effects, inadequate analgesia, or induction of withdrawal symptoms. As an alternative, the clinical development program examined the clinical utility of the dosage form as a substitute for the patients' standard morphine analgesic regimens.

As discussed in the previous section (Pharmacokinetic-Pharmacodynamic Correlations), an attempt was made to correlate the morphine plasma concentrations and analgesic response in patients with chronic cancer pain. As noted above, the expected association was found.

5. Other Pharmacological Effects

The pharmacologic actions of morphine are well-known, and aside from the analgesic studies presented in this application, no additional studies have been conducted to define the ancillary pharmacologic activities of morphine. The sponsor believes that the labeling for currently marketed morphine products, as adapted to the proposed labeling for Kadian™, contain an adequate description of the pharmacologic actions of morphine.

APPLICATION SUMMARY

7. CLINICAL DATA SUMMARY

B. Background/Overview of Clinical Investigations NDA Volume 59

1. Introduction

The clinical development program for Kadian™ Capsules was developed in association with the Pilot Drug Evaluation Staff of the Food and Drug Administration through the Interactive IND process. The program consisted of eleven pharmacokinetic studies and six clinical efficacy and safety studies that were designed to allow approval of the proposed labelling claims for Kadian™ Capsules.

Kadian™ morphine sulfate sustained-release capsules, 20mg, 50mg and 100mg, have been developed by F.H. Faulding & Co. Limited, an Australian pharmaceutical company, as a sustained-release oral formulation of morphine suitable for once or twice daily administration in the treatment of moderate to severe pain.

The first IND meeting was held with the Pilot Drug Evaluation Staff on 9 November 1990, prior to undertaking the first pharmacokinetic studies. This meeting provided the basis for a firm plan of single and multiple dose pharmacokinetic studies. However, the final design of the clinical efficacy and safety program was discussed only in general terms as many of the requirements for these studies would depend on the pharmacokinetic data generated.

The initial design of the Kadian™ clinical program was based on the following requirements:

- Pharmacokinetic data showing the pharmacokinetic profile of Kadian™ in comparison with other morphine products should be generated.

- Pharmacodynamic, efficacy and safety data would be required to demonstrate a full 12 hour duration of action compared to MS Contin® in two adequate and well-controlled studies.

The FDA also requested that surrogate efficacy parameters (i.e. pharmacodynamic measurements) should be investigated in the pharmacokinetic studies, that attention should be given to the intra- and

inter-subject variability in morphine pharmacokinetics, and that the morphine metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) should be profiled in the pharmacokinetic studies. At the 9 November 1990 meeting, Pilot Drug Evaluation Staff also provided the following input on the general design of the clinical program:

- That claims for Kapanol™ in comparison with MS Contin® could only be based on clinical trials that directly compared the two products.
- That efficacy trials should incorporate some pharmacodynamic measurements validated from pharmacokinetic studies.
- That several direct and indirect measures of efficacy should be used to compare onset of action and duration of action with those of MS Contin®.
- That rescue morphine should be used as an objective measure of onset, extent and duration of analgesia.
- That clinical trials should be designed to account for "baseline creep".

2. Initial Clinical Program

The initial clinical program consisted of four single dose pharmacokinetic studies, one multiple dose pharmacokinetic study and one clinical efficacy and safety study. The design of further clinical efficacy and safety studies was to be based on results from the pharmacokinetics studies.

The four single dose pharmacokinetic studies were designed to generate the following data:

a. The pharmacokinetics of Kadian™ fed and fasting in comparison with immediate-release morphine (IRM) solution fasting (MOBU-7/90-2).

b. The pharmacokinetics of Kadian™ in comparison with MST Continus® Tablets and IRM solution (KAP-RRC/91/01) (MST Continus® is the European and Australian trade name for MS Contin®, The Purdue Frederick Company, Norwalk, Connecticut.

c. The linearity of pharmacokinetics of Kadian™ across the dose range 30mg to 100mg (MOBU-9/90).

d. *In vivo* bioavailability data to validate the *in vitro* dissolution specifications of Kadian™ (MOB-10/90).

In accordance with Pilot Drug Evaluation Staff advice, the following pharmacodynamic measurements were incorporated into study MOBU-7/90-2: pupil diameter, nausea, sedation and respiratory function (respiratory rate, oxygen saturation, heart rate and end tidal carbon dioxide). These pharmacodynamic measurements were chosen to explore a potential pharmacokinetic - pharmacodynamic correlation in order to provide surrogate parameters of efficacy.

This first pharmacokinetic study completed 30 healthy subjects because of the intra- and inter-subject variability in morphine pharmacokinetics. The data from this study showed that 24 evaluable subjects would be sufficient for adequate statistical power in all subsequent studies.

The multiple dose study (MOB-1/90) was designed to compare the pharmacokinetics of Kadian™ with MS Contin® and IRM solution at steady state in patients with moderate to severe chronic cancer pain.

The initial clinical efficacy and safety study in 24 patients (MOBES-8/90) with moderate to severe chronic cancer pain compared IRM solution and Kadian™ in a two-way crossover study.

Results/Conclusions

The results of these first five pharmacokinetic studies and one clinical study showed the following:

- That, after a single oral dose, Kadian™ has a true sustained-release kinetic profile compared to MS Contin® and IRM solution.
- That food does not significantly affect the extent of absorption (AUC) of morphine from Kadian™ but does increase T_{max} slightly, although this is not clinically significant at steady state.
- That the pharmacokinetics of Kadian™ are linear across the dose range 30mg to 100mg.
- That the pharmacokinetics and molar metabolite to morphine ratios of M3G and M6G are not different in patients receiving Kadian™ compared to MS Contin® and IRM solution.
- That, at steady state, Kadian™ shows a true sustained-release pharmacokinetic profile with significantly lower percentage fluctuation in plasma morphine levels compared to both MST Continus® and IRM solution.

- That, at steady state, there is no statistically significant difference in the frequency of morphine-related side effects in patients receiving Kadian™ compared to patients receiving MS Contin® or IRM solution.

- That Kadian™ administered every 12 hours is effective in controlling pain in patients with moderate to severe chronic cancer pain and that no significant breakthrough pain occurs during transfer from IRM solution.

Although some of the pharmacodynamic measures did show dependence on plasma morphine levels, the presence of significant physiological lag times, plateau effects and substantial persistence of the effect following a decrease in plasma morphine levels, limited the usefulness of these measures. Therefore, they were not used as surrogate parameters of efficacy in clinical efficacy and safety studies.

3. Clinical Efficacy and Safety Studies **NDA Volume 59**

Data generated from the initial five (four single dose and one multiple dose) pharmacokinetic studies and one clinical efficacy and safety study were used to design a clinical program for US registration.

The clinical program was directed at establishing the following claims:

a. 12 hour Duration of Action

There was a high probability that a true 12 hour duration of action could be established with Kadian™ dosed every 12 hours because higher plasma levels of morphine were maintained out beyond 8 hours in comparison to MS Contin® in single dose studies, and there was significantly less fluctuation in plasma morphine levels with Kadian™.

b. Once Daily Dosing Regimen

Simulated steady state pharmacokinetic data for Kadian™ showed that the formulation might be suitable for once daily dosing. In comparison with MS Contin®, peak plasma morphine levels and trough plasma morphine levels would be comparable to those seen when MS Contin® was dosed every 12 hours. Kadian™ was therefore thought to be suitable for a once daily dosing regimen when the same total daily dose of morphine was administered once every 24 hours in the morning.

The objectives of the plan for clinical efficacy and safety studies were to show that:

a. Kadian™ given every 12 hours was at least as effective in maintaining pain control in patients with cancer pain as MS Contin® given every 12 hours.

b. Kadian™ given once daily was effective in maintaining pain control over 24 hours in patients with cancer pain.

c. Patients could be transferred safely and effectively from other morphine formulations to Kadian™.

d. Patients could be transferred from IRM solution to Kadian™ by administering the last dose of IRM solution with the first dose of Kadian™.

e. To investigate the morphine-related side effects and spontaneously reported adverse event profile with Kadian™ administered every 24 hours and every 12 hours.

To establish these objectives the Pilot Drug Evaluation Staff had indicated that the following design features would need to be incorporated into clinical studies:

- Data on 300 patients who had received Kadian™ in clinical studies and in a labelling validation study should be submitted (FDA meeting 18 September, 1991; FDA contact by Ms Josephine Dundon, 9 February, 1993; teleconference with Dr Curtis Wright, 12 March, 1993).

- Clinical studies should show that it is possible to transfer patients from other morphine formulations to Kadian™ and then from Kadian™ to other morphine formulations without adverse reactions and with sufficient efficacy (FDA meetings of 18 September, 1991 and 29 April, 1992).

- The most sensitive parameters to establish efficacy were total dose of rescue medication, time to remedication, investigator rating of pain, patient rating of pain, dropout rate (FDA meeting, 18 September, 1991).

- Efficacy studies should demonstrate that Kadian™ was efficacious compared to other morphine formulations in the clinical setting (FDA meeting, 18 September, 1991).

- Pilot Drug Staff also agreed that it was acceptable to use MST Continus® Tablets in the earlier studies. MST Continus® (Napp Laboratories) is the European and Australian trade name for MS Contin® (The Purdue Frederick Company).

In addition, consideration of the type and quantity of clinical data required was based on "Guidelines for the Clinical Evaluation of Analgesic Drugs", FDA (revised November 1990). Replicate evidence of efficacy in several studies was provided, more than one study site was used, and at least some of the studies were performed in the United States. All but one clinical efficacy study (MOR-5/92) was of double-blind design and the comparator drug, MS Contin®, had the same mechanism of action. Both parallel group and crossover studies were used. Data on onset of effect, peak effect, total effect and duration of effect were collected by means of pain scores on the final assessment day. Studies in outpatients incorporated detailed patient instruction to maximize compliance, validated assessments, close telephone contact with patients and meticulous follow-up. Both Investigator and patient global assessments of efficacy were used.

In consideration of these requirements the following studies were incorporated into the Kadian™ Clinical Program:

a. The comparative efficacy and safety of Kadian™ every 24 hours, Kadian™ every 12 hours and MS Contin® every 12 hours (CDD-14556).

b. Comparative pharmacokinetics and pharmacodynamics of Kadian™ every 24 hours, Kadian™ every 12 hours and MS Contin® every 12 hours (CDD-14922/MOR-2/92).

c. Safety and acceptability of transfer from IRM Solution and MS Contin® to Kadian™ (MOR-5/92).

d. Comparative pharmacokinetics and pharmacodynamics of Kadian™ every 24 hours and MS Contin® every 12 hours (MOR-9/92).

e. Long-term safety and efficacy studies (extension studies CDD-14785, CDD-15220, MOR-7/92 and MOR-10/92).

f. Labelling Validation Study.

Discussions with the Pilot Drug Evaluation Division indicated that for claims of "superiority", the FDA would want to see that the "therapeutic effect" of Kadian™ was superior to comparator morphine formulations and that the

side-effects were no worse at the time of peak plasma morphine levels than comparator products (FDA contact, Ms Josephine Dundon, 22 October, 1992).

"Superiority" was defined as an improvement in mean pain scores (either VAS or VRS pain scores) with treatment with Kadian™ in comparison with MS Contin®. The considerable inter- and intra-patient variability in plasma morphine levels and the poor correlation of these levels with pain control meant that it would be virtually impossible to demonstrate a clinically significant difference between Kadian™ and MS Contin® treatments. It was therefore, agreed within F.H. Faulding & Co. Limited, that we would not try to demonstrate that Kadian™ was "superior" in terms of efficacy to MS Contin®.

The pivotal studies were CDD-14556, CDD-14922/MOR-2/92 and MOR-9/92. They were to generate clinical efficacy and safety data for the Kadian™ q24h and Kadian™ q12h treatment regimens in comparison with MS Contin® q12h. However, CDD-14922/MOR-2/92 was prematurely closed because of a significant number of non-eligible and non-evaluable patients combined with the likelihood of continuing poor patient recruitment.

Studies CDD-14556 and MOR-9/92 were therefore the two pivotal, well-controlled studies. CDD-14556 was originally intended to be a double-blind comparison of the three active treatment regimens with placebo. However, enrolment was very slow because of patient concern with placebo treatment for chronic cancer pain. An interim analysis of the first 17 patients completed showed that there was a statistically significant difference for the active treatment groups combined compared to placebo for the primary efficacy parameters. Following consultation with the Pilot Drug Evaluation Staff, the protocol was amended eliminating the placebo treatment group. MOR-9/92 generated the definitive pharmacokinetic data on the Kadian™ q24h regimen and pharmacokinetic-pharmacodynamic correlations for Kadian™ q24h and MS Contin® q12h.

Studies MOBES-8/90 and MOR-5/92 provided supportive data for the NDA. Studies MOR-5/92, MOBES-8/90 and MOR-9/92 specifically looked at pain scores and morphine-related side effects on the first day of transfer of patients from IRM solution and MS Contin® to Kadian™. MOR-5/92 was an open-label study while MOBES-8/90 and MOR-9/92 were double-blind studies.

In MOBES-8/90, patients titrated to adequate analgesia with IRM solution took the first dose of Kadian™ four hours after the last dose of IRM solution. In all other studies, patients took the first dose of Kadian™ with the last dose of IRM solution or four hours after the last dose of MS Contin® (MOR-5/92 only).

All clinical studies with Kadian™ incorporated more than one critical measure of efficacy.

Primary efficacy parameters on the final assessment day of all studies were:

- time to first dose of rescue medication
- amount (mg) of rescue medication
- time to first remedication (whether rescue medication or study medication)

Secondary efficacy parameters were:

- Investigator global assessment of efficacy
- patient global assessment of pain control
- patient treatment preference (crossover study MOR-9/92 only)
- quality of sleep and pain assessments

Safety assessments included:

- morphine-related side effects (nausea/vomiting, constipation, sedation, confusion, appetite)
- adverse events
- clinical laboratory assessments

Long-term safety and efficacy studies maintained patients on Kadian™ treatment for up to 6 months (CDD-14785, CDD-15220) or for up to 12 months (MOR-7/92, MOR-10/92) or for up to 24 months (MOS 2/91/MOS3/91, MOR-3/92).

Results/Conculsions

The US clinical program generated data which supported the following conclusions:

a. In the management of moderate to severe chronic pain, Kadian™ administered both every 24 hours and every 12 hours has an efficacy profile clinically and statistically similar to that of MS Contin® q12h and IRM solution q4h when assessed using established measures of efficacy.

b. In those studies in which Patient Global Assessments of Pain Control were recorded, including both the controlled and uncontrolled clinical trials, pain control with Kadian™ q24h and q12h was graded as acceptable. In controlled studies which included comparator drugs, either IRM solution or MS Contin®, pain control was similar to that with Kadian™.

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c. In those studies in which Investigator Global Assessments of Efficacy were recorded, including both the controlled and uncontrolled clinical trials, investigators judged that Kadian™ q24h and q12h provided marked to moderate efficacy. Similar evaluations were obtained for IRM solution and MS Contin® in the controlled clinical trials that contained these comparator drugs.

d. When converting patients from IRM formulations, the first dose of Kadian™ should be given with the last dose of the immediate-release preparation.

e. In two double-blind, double-dummy crossover controlled clinical trials, studies MOBES-8/90 and MOR-9/92, there were no differences in the use of rescue medication on the first day of treatment with Kadian™ compared to the last day of treatment with IRM solution q4h. Therefore, patients stabilized to adequate clinical effect with other oral morphine formulations may be safely transferred to Kadian™ at the same total daily morphine dose.

f. During the long-term open-label studies of Kadian™ q12h, there was no indication of diminution of analgesia in patients with cancer pain treated for up to 24 months. Dose escalations that did occur were consistent with disease progression.

The standard subanalyses of age, sex and race were conducted for study CDD-14556. The Pilot Drug Evaluation staff had also indicated that, because patients with a morphine demand of less than 120mg/day may have a limited tolerance to opioids and limited sensitivity to changes in daily morphine dose, a subanalysis of the high dose versus low dose groups should also be undertaken. By agreement with the Principal Medical Reviewer, a cut off of 110mg/day was chosen because it divided the total population into two groups of approximately equal size (FDA meeting, May 1994). However, there was no statistically significant difference for either efficacy or safety parameters among each of the treatment groups.

4. Proposed Post-marketing Studies **NDA Volume 59**

Two post-marketing studies are currently proposed for Kadian™: a Labelling Validation Study to be conducted during NDA review, and an efficacy and safety study in children.

The Labelling Validation or Comprehension Study is to be conducted at the request of the Principal Medical Reviewer for Kadian™ in the FDA's Pilot Drug Evaluation Staff. The FDA had indicated that they would require information to validate the labelling claim for pain relief and to compare the safety profile and

adverse reactions with those that are normally expected for morphine formulations (FDA meeting, 29 April, 1992). The Principal Medical Reviewer indicated that the FDA would work with F.H. Faulding & Co. Limited to develop a "close to final labelling and packaging insert" (FDA contact, Ms Josephine Dundon, 29 October, 1992). The Labelling Validation Study would test the clinician's comprehension of the close-to-final draft labelling and would develop a data set representing the safety of the drug in actual clinical use.

The Labelling Validation Study will be conducted in 100 to 150 patients with moderate to severe chronic pain at 10 to 15 investigator sites in the US. Data will be collected on the following: patient diagnosis, previous medication for pain, other diseases, dose, interval and duration of treatment with Kadian™, adverse events, comparison with drugs of the same class, effectiveness of pain control and physician comprehension of the labelling. The study will start third quarter 1995 and will recruit patients over 6 to 9 months.

Because no controlled release morphine formulations have a labelling claim for use in children, Faulding anticipates undertaking a clinical development program directed at establishing efficacy and safety in this patient population. It is also proposed that a limited pharmacokinetic data also be generated.

The current design calls for a double-blind, randomized, crossover study comparing Kadian™ administered every 12 hours with Kadian™ administered every 24 hours in 24 children with moderate to severe chronic cancer pain. The study will be conducted at investigator sites in the US. Standard efficacy and safety data will be collected and the pharmacokinetic profile of morphine and its metabolites will be characterised in a sub-set of patients. The study design will be further developed in consultation with both FDA and investigators.

7. CLINICAL DATA SUMMARY

C. Clinical Efficacy Summary

The clinical program to be described was designed in close consultation with staff of the Pilot Drug Evaluation Staff of the FDA through the interactive IND process.

The studies that contribute data to the efficacy assessment are presented in Table 1. The table is divided into three parts on consecutive pages; Pivotal Clinical Trials, Supportive Controlled Clinical Trials, and Uncontrolled Trials. Kadian™ is a new sustained-release formulation of morphine sulfate in which the product is formulated as a capsule containing sustained-release pellets of morphine sulfate. Because morphine sulfate is a well-known analgesic, and pharmacokinetic and bioavailability studies have shown it to be absorbed from Kadian™ to the same extent as Immediate Release Morphine solution and MS Contin® with no evidence of dose dumping, all of the clinical studies conducted have been Phase III.

TABLE 1

Table of Studies
Pivotal Controlled Clinical Trials

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects	Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs 4) IND Ser. No. (vol/page)
Pilot CDD-14556	Completed, May 1, 1992 - May 1993	Randomized, double-blind, double-dummy parallel group in patients with moderate to severe cancer pain	Kapanol® Capsules, q24h Kapanol® Capsules, q12h MS Contin® Tablets, q12h Placebo Dose based on nearest appropriate total daily dose of IRM* solution or tablets from 3-14 day titration Lead-In Period. Duration: 7 days/period x 3 periods	Kapanol®, q24h: 4 Kapanol®, q12h: 6 MS Contin® 6 Placebo 6	53 ± 6.3 3M, 1F 3 W, 1 NW 62.5 ± 9.5 4 M, 2 F 4 W, 2 NW 59.5 ± 14.7 0 M, 6 F 5 W, 1 NW 50.7 ± 8.0 3 M, 3 F 5 W, 1 NW	1) **060 / 001** 2) **141 / 001** 3) **169 / 316** 4) **090**

* IRM = Immediate-release morphine

TABLE 1 (Cont'd)

Table of Studies
Pivotal Controlled Clinical Trials

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects	Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs 4) IND Ser. No. (vol/page)
CDD-14556 30 Centers in the United States Dr. R. O. Kerr, PI	Completed, May 19, 1992 - March 7, 1994	Randomized, double-blind, double-dummy, parallel group in patients with moderate to severe cancer pain	Kapanol® Capsules, q24h Kapanol® Capsules, q12h MS Contin® Tablets, q12h Dose based on nearest appropriate total daily dose of IRM* solution or tablets from 3-14 day titration Lead-In Period. Duration: 7 days/period x 3 periods	Kapanol®, q24h: Randomized 61 Treated 61 Completed: 54 Kapanol®, q12h: Randomized 55 Treated 55 Completed: 45 MS Contin™, q12h: Randomized 56 Treated 56 Completed 53	60.4 ± 12.3 30 M, 31 F 47 W, 14 NW 61.2 ± 12.8 35 M, 17 F 41 W, 11 NW 61.4 ± 12.9 28 M, 28 F 44 W, 12 NW	1) **060 / 001** 2) **141 / 001** 3) **169 / 316** 4) **090**
MOR-9/92 Australia Dr. D. Cherry	Completed, July 15, 1993 - Dec. 30, 1994	Randomized, double-blind, double-dummy, 2 period crossover in patients with moderate to severe cancer pain	Kapanol® Capsule, q24h MS Contin®, q12h Duration: 7 days/period x 2 periods	Total randomized: 29 Treated 29 Completed crossover: 25	64.9 ± 13.2 18 M, 11 F 29 W, 0 NW 65.2 ± 13.0 16 M, 9 F 25 W, 0 NW	1) **077 / 001** 2) **140 / 001** 3) **155 / 192** 4) **092**

* IRM = Immediate-release morphine

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TABLE 1 (Cont'd)

Table of Studies
Supportive Controlled Clinical Trials

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects	Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs 4) IND Ser. No. (vol/page)
MOBES-8/90 3 centers in Australia Dr. J.F. Bishop Dr. J. Levi Dr. T. Cramond	Completed April 10, 1991 - May 29, 1992	Randomized, double-blind, double-dummy, 2 period crossover with 12 week open-label extension	Kapanol® Capsule, q12h IRM* Sol., q4h Treatment Period: Crossover: 7 days/period x 2 periods Open-label: 12 wk	Total randomized: 27 Treated: 27 Completed crossover: 24 Entered open-label: 20 Completed: 10	60 ± 12 19 M, 8 F 26 W, 1 NW 61 ± 12 16 M, 8 F 23 W, 1 NW 61 ± 13 13 M, 7 F 20 W, 0 NW	1) **086 / 001** 2) **146 / 209** 3) **153 / 104** 4) **040**

* IRM = Immediate-release morphine

000234

TABLE 1 (Cont'd)

Table of Studies
Supportive Controlled Clinical Trials

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects	Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs 4) IND Ser. No. (vol/page)
MOR-2/92 United States Dr. R.K. Portenoy Dr. K. M. Foley	Study terminated prior to completion due to poor recruitment & control of procedures. January 29, 1993 - December 19, 1993	Randomized, double-blind, double-dummy, balanced incomplete block 2 period crossover design in patients with moderate to severe chronic pain.	Kapanol®, q24h Kapanol®, q12h MS Contin®, q12h Treatment: 7 days/period x 2 periods	Number enrolled: 19 Randomized: 18 Treated: 18 Completed: 16 Number evaluable: 6	47.5 (23 - 71) 7 M, 12 F 17 W, 2 NW	1) **076 / 001** 2) **147 / 174** 3) **157 / 001** 4) **087**
MOB-1/90 Australia Dr. David A. Cherry	Completed April 4, 1991 - July 2, 1992	Randomized, open-label, three-period crossover in patients with moderate to severe cancer pain	Kapanol®, q12h MST Continus®, q12h IRM* Sol., q4h Treatment: 7 days/period x 3 periods	Entered: 50 Randomized: 34 Treated: 34 Completed: 24	64.6 ± 10.7 36 M, 14 F 50 W, 0 NW	1) **027 / 001** 2) **138 / 001** 3) **150 / 131** 4) **064**

* IRM = Immediate-release morphine

000235

TABLE 1 (Cont'd)

Table of Studies
Uncontrolled Clinical Trials

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects	Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs 4) IND Ser. No. (vol/page)
MOS-1/91 3 centers in Australia Dr. D. Cherry Dr. G. K. Gourlay Dr. J. Plummer	Completed May 8, 1992 - September 17, 1992	Open-label, long-term study of safety and efficacy of Kapanol®. Twelve-week open-label extension to Study MOB-1/90	Kapanol®, q12h Treatment: 12 wk	Entered: 19 Completed: 9	62.8 ± 10.2 14 M, 5 F 19W, 0 NW	1) **088 / 001** 2) **148 / 030** 3) **157 / 239** 4) **075**
MOS-2/91 and 3/91 4 centers in Australia Dr. J.F. Bishop Dr. J. Levi Dr. T. Cramond Dr. D. Cherry	Completed July 24, 1991 - March 3, 1993	Open-label, long-term study of safety and efficacy of Kapanol®. Nine month open-label extensions of Studies MOS-1/91 and MOBES 8/90, respectively. Data presented together as one study.	Kapanol®, q12h Duration: 9 months	Entered: 29 Completed: 8	64.6 ± 10.7 24 M, 5 F Race distribution unspecified	1) **089 / 001** 2) **148 / 121** 3) **159 / 001** 4) **081**

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TABLE 1 (Cont'd)

Table of Studies
Uncontrolled Clinical Trials

Protocol Number, Location of Study, Investigators	Study Status, Dates of Study	Study Design	Treatment, Dosage Regimen, Duration of Treatment	Number of Subjects Treated	Age (Mean ± SD) Gender (#M, F), Race (#W, NW)	Location of: 1) Study Rpt. 2) CRF Tabs 3) CRFs 4) IND Ser. No. (vol/page)
MOR-3/92 2 centers in Australia Dr. T. Cramond Dr. D. Cherry	Completed June 18, 1991 - Nov. 16, 1993	Open-label, long-term study of safety and efficacy of Kapanol®. Twelve month open-label extension of Studies MOS-2/91 and 3/91 in two of the four study sites.	Kapanol®, q12h Duration of Treatment: 12 months Duration: Intended to be 12 mo., but discontinued early due to low number of remaining patients.	Enterered: 7 Completed: 1	57.4 ± 10.4 5 M, 2 F Race distribution unspecified	1) **089 / 001** 2) **148 / 121** 3) **159 / 001** 4) **081**
MOR-5/92 8 centers in Australia Dr. Ian Olver, PI	Completed June 7, 1993 - June 9, 1994	Open-label, randomized, parallel switch study	Kapanol®, q12h Kapanol®, q24h Duration of Treatment: 7 days	Enrolled: 49 Randomized: 41 Treated 41 Completed: 37	63.4 ± 13.3 27 M, 14F 39 W, 2 NW	1) **092 / 001** 2) **139 / 001** 3) **164 / 142** 4) **091**

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1. Identification of Adequate and Well-Controlled Clinical Trials

Based on meetings with the Pilot Drug Evaluation Staff, several requirements regarding the types of studies and data that would be necessary for approval were identified. These requirements are summarized below:

- Pharmacokinetic data showing the pharmacokinetic profile of Kadian™ in comparison with other morphine products would be required.
- Pharmacokinetic data and concurrent collection of pharmacodynamic data were determined to be important to a q24h labeling claim.
- We would need to demonstrate that morphine-related side effects were no worse at the time of peak blood concentration and that pain control was no worse at the time of trough blood levels.
- Efficacy data demonstrating that patients can be transferred from other opioids to Kapanol® safely and effectively should be generated.

The most sensitive parameters of efficacy for use in analgesic studies were determined to be:

- time to use of first rescue medication;
- total amount of rescue medication required;
- patient rating of pain control; and
- patient and investigator global assessments.

2. Design, Results and Analysis of Pivotal Clinical Trials

Two studies, CDD-14556 and MOR-9/92, were selected as pivotal studies. As noted in Table 1, both studies were randomized, double-blind comparisons of Kadian™ q12h, Kadian™ q24h, and MS Contin® q12h in patients with moderate to severe cancer pain. Because CDD-14556 was a parallel group study and MOR-9/92 was a crossover study, the results were not combined. Each study is considered to stand on its own merits.

The primary efficacy parameters measured were based on the amount of rescue medication taken during the final 24 hours of each 7-day treatment period (Final Day). The variables included:

- The time to first remedication was defined as the hours between the morning dose of study medication and the next dose of active medication whether it was rescue or the next regularly scheduled dose of double-blind medication.

- The elapsed time to rescue on the Final Day was defined as the number of hours from the morning dose of study medication to the first dose of rescue medication. Patients were followed for up to 24 hours or until they took study medication on the morning of the following day, whichever was the shorter interval. Patients who did not need rescue medication were assigned a score of 24 hours.

- Total amount of rescue medication taken in the 24 hours of Final Day. The amount was converted to milligrams and the percent of the final titrated dose of IRM solution taken in the Lead-In Period.

Included in the secondary measures of efficacy were patient ratings of pain intensity and control using a visual analogue scale (VAS), a 100 mm line on which patients marked the intensity of pain ranging from 0, representing no pain, to 100, representing worst possible pain; a 4-point verbal rating scale (VRS) for pain control (0=Complete, 1=Partial, acceptable, 2=Partial, unacceptable, 3=No pain control at all); and a 5-point VRS for pain intensity (0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Intolerable). Patients were also asked to assess quality of sleep with a 4-point VRS (0=Slept very well, 1=Slept quite well, 2=Slept poorly, 3=Did not sleep at all). The patient global assessment of effectiveness was a 4-point VRS (Very Good, Good, Fair, Poor). The investigator's global assessment of efficacy was a 4-point VRS (0=Marked efficacy, 1=Moderate efficacy, 2=Minimal efficacy, 3=No efficacy).

a. Study CDD-14556 **NDA Volume 60**

This was a randomized, double-blind, double-dummy parallel group comparison of Kapanol® q24h, Kapanol® q12h, and MS Contin® q12h in patients with moderate to severe cancer pain.

Prior to the beginning of the double-blind treatment period, each patient was titrated to a stable total daily dose of IRM solution or tablets. At the end of the Lead-In Period, qualified patients were randomly assigned to a 7-day treatment period with one of the three active drug regimens. For the 7-day treatment period, a double-dummy system was used to dispense a double-blinded total daily dose of active medication equivalent to the final total daily dose of IRMS required to control pain during the Lead-In Period. Morning and evening doses were individually packaged. Patients assigned to the Kapanol® q24h treatment received the active medication for the morning dose and placebo for the evening dose. For the other treatments the total daily dose was equally divided between morning and evening.

In addition, IRMS tablets were dispensed to all patients for breakthrough pain. Patients were instructed to take approximately 1/8 of the total daily dose for breakthrough pain at two to four hour intervals as needed.

Pilot CDD-14556

The study was originally intended to be a double-blind comparison of four treatments (Kapanol® q24h, Kapanol® q12h, MS Contin® q12h, and placebo). One hundred patients were to be included in each treatment group, including the group receiving placebo. Even though each patient was to be given a supply of IRMS tablet rescue medication, enrollment was very slow because study candidates were concerned about the possibility of poor pain control on treatment with placebo. Data from 17 patients who had completed the study were collected and analyzed to provide a basis for recommending sample size for an amended study with only the three active treatments. A summary of that analysis follows (See Appendix 1.4 of the study report for CDD-14556.).

Table 2
Mean Primary Efficacy Responses (Pilot-CDD-14556)

Variable	Kapanol® q24h	Kapanol® q12h	MS Contin® q12h	Placebo	p-value*
Number	3	5	5	4	
Elapsed time to remedication (hrs)	17.4	11.9	6.8	4.6	**0.0334**
Rescue on Final Day (mg)	10.0	3.0	13.5	82.5	**0.0006**
Rescue on Final Day (%IRMS)	5.56	2.50	11.91	56.25	**0.0001**

*F-test from ANOVA for difference among treatments.

Tukey's Studentized Range test (alpha = 0.05) indicated that Kapanol® q24h had a significantly longer time to remedication than placebo and that all active treatments (Kapanol® q24h, Kapanol® q12h, MS Contin® q12h,) required significantly less rescue medication than placebo, whether measured in milligrams or as a percentage of the final titrated Lead-In IRMS dose.

The results showed that the study design could separate placebo from active, that the active treatments were effective, and that the time to remedication and the amounts of rescue medication taken on the Final Day were sensitive surrogate measures of analgesic effect.

After consultation with the Pilot Drug Evaluation Staff at the Food and Drug Administration the protocol was amended eliminating the placebo treatment group.

Study CDD-14556

The amended study was a randomized, double-blind, double-dummy parallel group study of the relative efficacy and safety of Kapanol® and MS Contin® in the management of moderate to severe cancer pain during a 7-day treatment period. Patients were to receive Kapanol® administered at 12 or 24-hour intervals, or MS Contin® administered every 12 hours. Enrollment was to continue until 150 patients had completed the efficacy assessments on the last day of the Treatment Period.

One hundred and seventy-two patients were randomized to treatment in 28 centers; three patients were terminated before taking the blinded study medication and 17 were withdrawn during the Treatment Period primarily due to adverse events. One hundred and fifty-two patients completed the study: 54 patients who received Kapanol® q24h, 45 patients who received Kapanol® q12h, and 53 patients who received MS Contin® q12h. The daily titrated morphine doses from the Lead-In Period for patients in the three treatment groups who completed the study are presented in Table 3.

TABLE 3
Daily Morphine Requirements (Study CDD-14556)

Titrated Morphine Level (mg/day)	Kapanol® q24h	Kapanol® q12h	MS Contin® q12h
< 110 mg/day	29 (54%)	23 (51%)	30 (57%)
≥ 110 mg/day	25 (46%)	22 (49%)	23 (49%)
Number of Patients	54	45	53
No. of Patients with Morphine Req. > 110	25 (46%)	22 (49%)	23 (43%)
Mean ± SD	134.8 ± 143.8	141.2 ± 117.8	138.5 ± 118.0
Median	90.0	90.0	96.7

There were no differences in either the mean total daily morphine requirements or the distribution of requirements among the treatment groups. Overall, about 46% of the patients had a total daily morphine requirement of least 110 mg/day. In general, patients with a morphine demand less than about 120 mg/day have only a limited tolerance to opioids and limited sensitivity to changes in daily morphine dose. Patients with a morphine requirement of 120 - 240 mg/day are both tolerant and moderately sensitive to both under-analgesia and withdrawal, while patients requiring more than 240 mg/day of morphine are highly tolerant and very sensitive to withdrawal if a non-equivalent dose of morphine is given. The present population of patients would be expected to have developed some tolerance to morphine and would be at least moderately sensitive to morphine withdrawal, providing sensitivity to uncover potential cases of underdosing.

Data related to the primary efficacy parameters for all patients who completed the study are summarized in Table 4.

TABLE 4
Primary Efficacy Variables (Study CDD-14556)

Variable	Kapanol® q24h	Kapanol® q12h	MS Contin® q12h	p-values (a) Site	p-values (a) Trt.
Number of Patients					
Total	54 (100%)	45 (100%)	53 (100%)		
Not needing rescue	29 (54%)	22 (49%)	24 (45%)		0.682
Needing rescue	25 (46%)	23 (51%)	29 (55%)		
Elapsed Time (hr) to Remedication					
Mean	16.0*	9.1	8.7	0.383	0.001
95% CI (b)	14.3, 17.8	7.1, 11.0	6.9, 10.5		
First Rescue					
Mean	16.0	15.6	14.3	0.215	0.934
95% CI (b)	13.5, 18.6	12.8, 18.3	11.8, 16.9		
Total Rescue in 24 Hr mg					
Mean	25.1	22.0	27.7	0.636	0.930
95% CI (b)	12.0, 38.2	7.9, 36.1	14.6, 40.8		
% IRM (c)					
Mean	17.3	14.9	23.1	0.912	0.571
95% CI (b)	7.5, 27.1	4.4, 25.4	13.3, 32.9		

(a) P-values are from chi-square tests of F test from ANOVA for site effect (Site) and treatment effect (Trt).
(b) The 95% CI (confidence interval) was computed using the mean squared error from the ANOVA.
(c) % IRM is percent of the titrated daily immediate-release morphine sulfate dose level.
(*) Indicates mean is significantly ($p<0.05$) different from that of MS Contin® q12h by Dunnett's t-test.

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The results reported above indicate that the time to remedication with active medication for the Kapanol® q24h group was significantly longer than that for MS Contin®, similar to the results of the Pilot CDD-14556. However, because this may be an artifact of differences in the timing of active doses, comparisons were based on time to first rescue and the amount of rescue taken on the Final Day. These measure did not show a significant difference among the treatments. Comparison of the amount of rescue in Table 4 with the Pilot CDD-14556 (Table 2) shows a higher level of rescue with more variability in all treatment groups. The active treatments in CDD-14556 still require less rescue medication than the placebo patients in the Pilot.

Results for patient rating of pain intensity are presented in Table 5 below. In the event a patient took rescue medication, the last observation just prior to the first dose of rescue medication was carried forward.

TABLE 5
Patient Rating of Pain Intensity and Control
(Study CDD-14556)

	Visual Analog Scale (VAS) for Pain Intensity		
Hours from AM Dose	Kapanol® q24h (n=52)	Kapanol® q12h (n=44)	MS Contin® q12h (n=52)
0	18.8	21.6	28.2
2	13.8	19.9	22.6
4	16.2	19.9	22.4
6	17.3	20.8	23.1
8	18.5	21.2	24.2
10	18.2	21.4	24.3
12	21.0	21.3	20.9
24	19.0	20.5	22.9

The differences in the VAS scores among treatment groups at each time point were not statistically different when tested by ANOVA. Although the differences were not significant, the two Kapanol® dosage regimens demonstrated consistently lower pain intensities on the VAS scale. The results from the VRS scores were similar.

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Results of the quality of sleep assessments and of the patient and investigator global assessments on the final day are presented in Table 6.

TABLE 6
Quality of Sleep and Global Assessments on the Final Day (Study CDD-14556)

Assessment	Kapanol® q24h	Kapanol® q12h	MS Contin® q12h
Quality of Sleep (% with "Very Good" or "Quite Good")	81	75	69
Patient Global Assessment (% rating treatment "Good" or "Very Good")	89*	76	68
Investigator Global Assessment (% "Marked" or "Moderate Efficacy")	94	87	85

* Fisher's Exact Test: $p<0.05$.

There were no statistically significant differences among the groups with respect to quality of sleep or the investigator global assessment, although the trends favored the Kapanol® groups over MS Contin®. The global assessment in which the patients evaluated their own pain control demonstrated a significantly better rating for Kapanol® q24h than for MS Contin®.

b. Study MOR-9/92 **NDA Volume 77**

Study MOR-9/92 was a randomized, double-blind, double-dummy, two-period crossover comparison of Kapanol® capsules q24h with MS Contin® tablets q12h in patients with moderate to severe cancer pain. The same primary and secondary efficacy measures were collected on the Final Day of each of the two 7-day treatment periods as those collected in Study CDD-14556. An additional objective was to collect morphine concentration data, to investigate any correlations between pharmacokinetic and pharmacodynamic variables.

As in CDD-14556, each patient was titrated to a stable dose of IRM solution during a 3 - 14 day Lead-In Period. Following Lead-In, qualified patients were randomly assigned to one of the two treatment groups. During the crossover portion of the trial, study medication was dispensed using a double-blind, double-dummy system to achieve blinded total daily doses of active study medications equivalent to the final total daily dose of IRM solution required to control pain during the Lead-in Period.

In addition to the study medication, all patients were dispensed dextromoramide tartrate 5 mg tablets (Palfium®, Faulding Pharmaceuticals) to be taken in the event of breakthrough pain.

Blood samples were collected on the mornings of Days 5 and 6 of each treatment period to determine if steady-state plasma morphine concentrations had been achieved. On the Final Day of each period (Day 7 ± 1) patients reported to the clinic and were confined for at least 24 hours for collection of 19 blood samples. Also, the following information was recorded: time to first rescue, total rescue taken, and patient rating of pain (at times coinciding with the blood draws). Following the second 24-hour confinement, patient and physician global assessments were obtained.

The titrated dose of IRM solution during the Lead-In Period for all patients who completed the study is presented in Table 7.

TABLE 7
Daily Morphine Requirements (Study MOR-9/92)

	Dosing Sequence		
	1 (a)	2 (b)	Overall
n =	12	12	24
IRM Dose (mg/day)	232.5 ± 321	165.3 ± 228	198.9 ± 275
Dose < 110 mg/day	5	8	13
Dose ≥ 110 mg/day	7	4	11

Data are reported as the mean ± SD.
(a) Sequence 1 = 7 days on Kapanol® q24h followed by 7 days on MS Contin® q12h.
(b) Sequence 2 = 7 days on MS Contin® q12h followed by 7 days on Kapanol® q24h.

There was no statistically significant difference between the two treatment sequences. The mean morphine requirement of about 200 mg/day assured inclusion of patients with a dosage requirement of at least 120 to 240 mg/day who were likely to be tolerant to morphine and at least moderately sensitive to under-analgesia and morphine withdrawal.

Results of the primary efficacy parameters on the Final Day of the two treatment periods combined for each treatment are provided in Table 8. Data for each treatment group were pooled across treatment sequences since there were no sequence or period effects in the ANOVA for any of the comparisons examined.

TABLE 8
Primary Efficacy Variables (Study MOR-9/92)

	All Completed Patients	
	Kapanol® q24h	MS Contin® q12h
Number of Patients	24 (100%)	24 (100%)
Not Needing Rescue	14 (58%)	11 (46%)
Needing Rescue	10 (42%)	13 (54%)
Elapsed Time (hr) to:		
Remedication		
Mean	16.8 (a)	8.6 (a)
95% CI	14.3, 19.3	6.2, 11.1
First Rescue		
Mean	16.8	14.3
95% CI	14.1, 19.5	11.6, 17.0
Total Rescue in 24 Hours		
mg		
Mean	5.0	5.2
95% CI	3.0, 7.0	3.2, 7.2
% of IRM (b)		
Mean	4.4	4.9
95% CI	2.5, 6.3	3.0, 6.7

(a) $p < 0.0001$. P-values are from test of ANOVA for sequence effect, study period effect and treatment effect.
(b) % IRM is percent of the titrated daily immediate-release morphine sulfate dose level.
(c) $p < 0.05$.

Of the 24 patients who completed the study, 10 (42%) needed rescue medication while receiving Kapanol® q24h compared to 13 (54%) who needed rescue medication while on MS Contin® q12h treatment.

The mean time to remedication was significantly longer in the Kapanol® q24h group (16.8 hours) than it was in the MS Contin® q12h group (8.6 hours). The mean time to the first rescue dose for the Kapanol® q24h group (16.8 hours) was not statistically different from that of the MS Contin® q12h group (14.3 hours). There were no other statistically significant treatment differences between the treatments with respect to the primary efficacy variables. These results are similar to those observed in CDD-14556.

Scores on the VAS for the 24-hour period of the Final Day are presented in Table 9. The VAS scores in the Kapanol® q24h group remained constant until 3 or 4 hours after the morning dose when pain intensity decreased from 14.5 to 12.2 mm, representing a drop of 16%. The level remained at or below this level until 14 to 16 hours after the morning dose. VAS scores on the MS Contin® remained at baseline levels until 5 hours after the morning dose and returned to the baseline levels by 11 hours. There were 6 consecutive hours of lower VAS scores for the MS Contin® group compared to 8 to 10 hours for the Kapanol® q24h group.

TABLE 9
VAS for Pain Intensity (Study MOR-9/92)

Hours from AM Dose	Kapanol® q24h (n=24)	MS Contin® q12h (n=24)
0	15.3	14.6
1	13.7	11.8
2	13.3	13.2
3	14.5	15.2
4	12.2	14.0
5	11.0	11.6
6	10.3	12.8
7	9.6	12.1
8	10.1	12.0
9	9.6	12.3
10	10.0	12.3
11	11.4	14.5
12	10.5	13.8
14	12.2	16.8
16	13.0	13.9
18	14.1	15.5
20	13.5	13.1
22	14.1	12.3
24	10.9	12.8

There were no significant sequence or period effects for the two treatment groups. In addition, there was no time by treatment interaction and the differences between the two treatment groups were not significant either for the data as a whole or at each time of assessment. The mean pain scores for Kapanol® q24h were numerically lower than those for MS Contin® q12h from 4 hours to 20 hours after dosing, however throughout this period, the mean scores were within a few millimeters indicating that there was no clinically significant difference between treatments. Similar non-significant differences between treatment groups were found with the VRS scales for pain intensity and pain control.

The final secondary efficacy parameters were the global assessments by the patients and the investigators. These are summarized in Table 10.

TABLE 10
Global Assessments (Study MOR-9/92)

Assessment	Kapanol® q24h (n = 24)	MS Contin® q12h (n = 24)
Patient Global Assessments (% rating treatment "Good" or "Very Good"	16 (67%)	21 (85%)
Patient Preference		
Preferred Kapanol® q24h	17%	
Preferred MS Contin® q12h		46%
No Preference (38%)		
Investigator Global Assessments Patients with Marked or Moderate Efficacy	21 (87%)	22 (91%)

The results indicate that 67% of patients receiving treatment with Kapanol® q24h and 88% of patients receiving treatment with MS Contin® q12h rated their treatment as either good or very good. These differences were not statistically significant. The investigator global assessment revealed that efficacy for 88% of patients receiving treatment with Kapanol® q24h was graded moderate to marked while efficacy for 91% of patients receiving treatment with MS Contin® q12h was graded moderate to marked. These differences were also not statistically significant.

Patient preference for treatment was somewhat variable when assessed at the end of the two treatment sequences. Overall, 17% of the patients preferred Kapanol® q24h, 46% preferred MS Contin® q12h, and 38% expressed no preference.

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The comparison of the VAS and VRS scores between Kapanol® q24h and MS Contin® q12h on the first day of treatment following the Lead-In Period and the first day of transfer from Treatment Period One to Treatment Period Two is presented in Table 11.

TABLE 11
Use of Rescue Medication During Transfer from Lead-In to Treatment Period 1 and During Transfer from Treatment Period 1 to Period 2 (Study MOR-9/92)

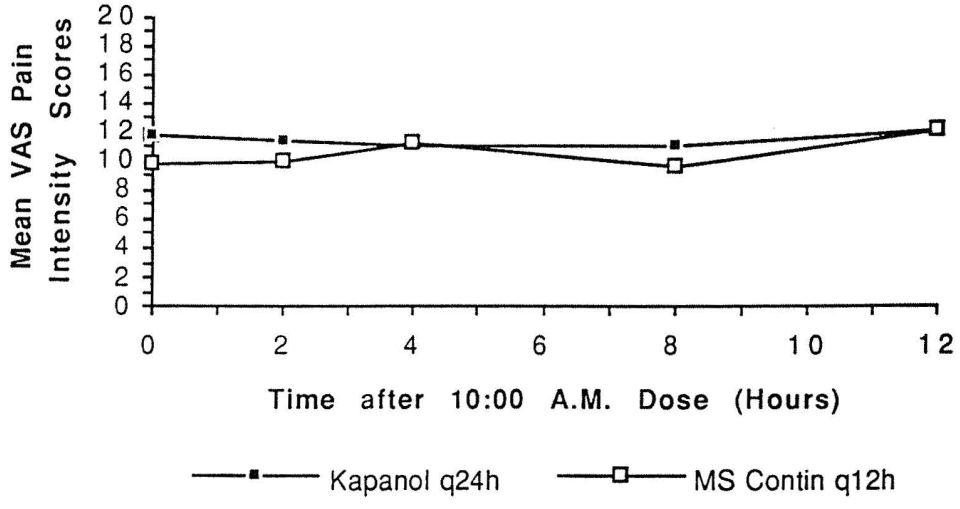
	Lead-In Period to Treatment Period 1		Treatment Period 1 to Period 2	
Use of Rescue Medication	Kapanol® q24h	MS Contin® q12h	Kapanol® to MS Contin®	MS Contin® to Kapanol®
Yes [No. (%)]	0 (0%)	3 (25%)	5 (42%)	5 (42%)
No [No. (%)]	12 (100%)	9 (75%)	7 (58%)	7 (58%)

There was no statistically significant difference between the Kapanol® q24h and MS Contin® q12h treatment groups in the percentage of patients using rescue medication on the first day of transfer from IRM solution, or the first day of transfer from Kapanol® to MS Contin®, or the first day of transfer from MS Contin® to Kapanol®.

Mean VAS scores on the first day of transition from IRM solution to Kapanol® q24h and MS Contin® q12h are presented in Figure 1.

FIGURE 1. Results of VAS Scores for Pain Intensity for Kapanol® q24h and MS Contin® q12h on the First Day of Treatment Period One (Study MOR-9/92).

The mean pain intensity scores are presented in millimeters inscribed by patients on a 100 mm scale where 0 indicates no pain and 100 represents the worst possible pain.



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There were no significant differences in VAS pain scores on the first day of Treatment Period One compared to the last day of Lead-in or the first day of Treatment Period One. There was no tendency to greater pain intensity over the course of the day. Similar results were obtained with the VRS scores.

Standard pharmacokinetic concentration parameters were computed from the morphine concentration data obtained from the 19 steady-state samples collected on the Final Day of each period. The concentrations were standardized to a 100mg/day dose before the parameters were computed. The parameters were:

- The fluctuations over the 24-hour blood sampling period

  $F1 = (C_{max} - C_{min})/C_{min}$

  $F2 = (C_{max} - C_{min})/C_{ave}$

  where: $C_{ave} = AUC_{0\text{-}24h}/t$, and t = dosing interval;

- The area under the plasma concentration versus time curve for the 24-hour blood sampling period ($AUC_{0\text{-}24}$) using the trapezoidal rule;

- The observed maximum plasma concentration (C_{max}) for the 24-hour blood sampling period;

- The time to reach the observed maximum plasma concentration (T_{max}) for the 24-hour blood sampling period, with the maximum effect (E_{max}) computed from the most recent dosing time for MS Contin®;

- The time period for which the observed plasma drug concentration is greater than or equal to 0.75 of C_{max} ($T_{\geq 0.75\ Cmax}$) for the 24-hour blood sampling period (WIDTH);

- The observed minimum plasma concentration (C_{min}) for the 24-hour blood sampling period.

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Standard comparisons using a crossover analysis of variance were done. The results are summarized in Table 12.

Table 12
Mean Steady-State Pharmacokinetic Parameters for Kapanol q24h and MS Contin q12h Adjusted to 100mg Dose Level (MOR-9/92)[a]

PK Parameters	Kapanol® q24h	MS Contin® q12h	p-Value
AUC_{0-24} (ng*hr/mL)	500.9 ± 193.2	457.3 ± 183.7	0.0202
Cmax (ng/mL)	37.3 ± 14.0	36.9 ± 15.5	0.8739
T_{max} (hr)	10.25 ± 3.30	4.42 ± 2.34	0.0001
C_{ave} (ng/mL)	20.9 ± 8.0	19.1 ± 7.7	0.0202
C_{min} (ng/mL)	9.9 ± 5.2	7.6 ± 4.6	0.0007
FLUCT1	3.0 ± 1.4	4.1 ± 2.1	0.0328
FLUCT2	1.4 ± 0.4	1.6 ± 0.5	0.0476
WIDTH (hr)	6.0 ± 3.0	4.8 ± 2.8	0.1727

[a] Data are presented as the mean ± SD for 24 evaluable patients.

Morphine levels following treatment with Kapanol® q24h showed a distinctly different profile over the 24-hour dosing interval compared with MS Contin® q12h. Although both treatments had numerically similar AUC_{0-24} and C_{max} values, Kapanol® q24h produced greater C_{min}, T_{max}, and WIDTH values compared to MS Contin® q12h. In addition, Kapanol® q24h produced reduced fluctuation indices compared with MS Contin® q12h over the 24-hour dosing interval which suggested that Kapanol® provided an enhanced sustained-release of morphine compared to MS Contin®.

The plasma metabolite to morphine ratios were similar for the two treatments, indicating that neither the dosage form nor the dosage interval altered the metabolism of morphine.

Figures 2 and 3 show the hourly mean morphine concentration and the hourly mean VAS scores on the Final Day of treatment. By comparing the two figures a sense of the relationship between concentration and response can be obtained. For MS Contin®, peak levels are reached by 4 hours, the same time that the pain intensity begins to decrease. By hour 11, MS Contin® concentrations are at trough levels and pain intensity has returned to baseline levels. In the Kapanol® q24h group concentration levels are slightly below MS Contin® in the first 4 hours; but they are sufficiently high that the pain intensity begins to lessen by 3 or 4 hours. The pain intensity drops and remains low until 16 to 18 hours after the morning dose when the concentration levels are beginning to decline.

FIGURE 2. Mean Plasma morphine concentrations at steady-state for Kapanol® q24h and MS Contin® q12h for 24 Patients with Evaluable Data (Study MOR-9/92).

Plasma concentrations have been adjusted to 100 mg dose level for purposes of comparison.

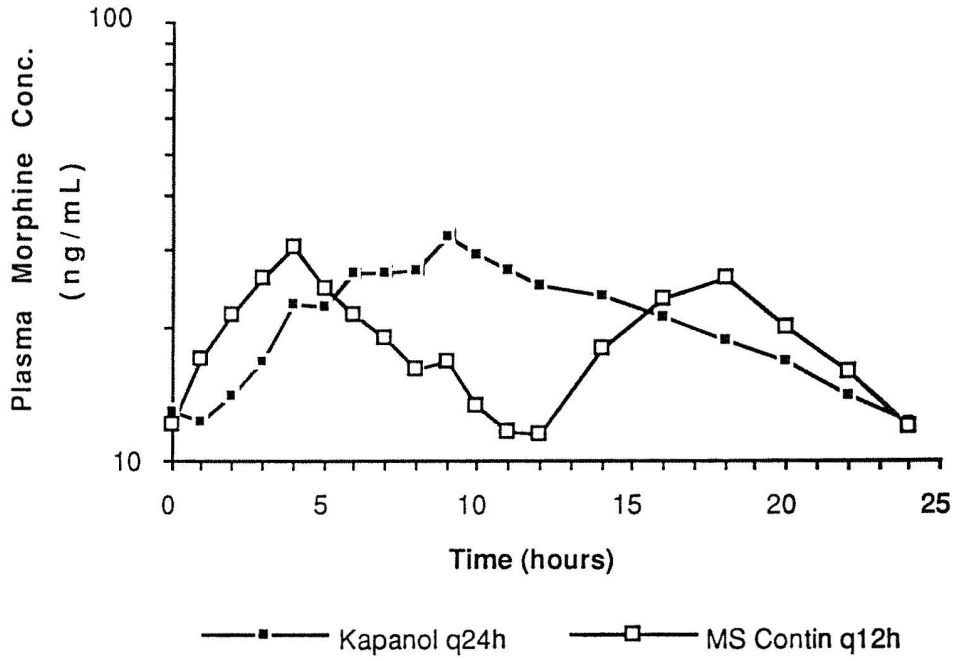
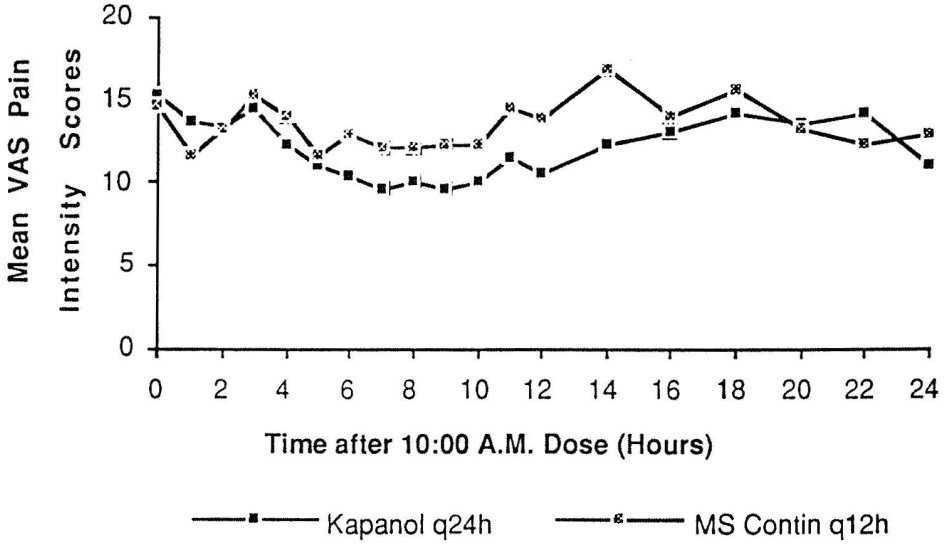


FIGURE 3. Results of VAS Scores for Pain Intensity for Kapanol® q24h and MS Contin® q12h on the Final Day of Treatment (Study MOR-9/92).

The mean pain intensity scores are presented in millimeters inscribed by patients on a 100 mm scale where 0 indicates no pain and 100 represents the worst possible pain.



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In addition, non-linear pharmacokinetic/pharmacodynamic (PK/PD) models were fit to describe the relationship between the response, defined as (100 - VAS)/100, and predicted concentrations of morphine at the effect site. The concentration of morphine in plasma that results in a half-maximal response (EC_{50}), the steepness of the response-concentration profile (gamma), and the transfer constant (K_{eo}) were estimated. Results of these analyses are reported in Table 13.

TABLE 13
Mean Steady-State Pharmacokinetic/Pharmacodynamic Parameters for Kapanol® q24h and MS Contin® q12h (Study MOR-9/92)[a]

PK/PD Parameter	Kapanol® q24h	MS Contin® q12h
Number of Patients with Evaluable Data	14	14
EC_{50} (ng/mL)[b]	0.27 ± 0.59	0.68 ± 1.24
K_{eo} (1/hr)[c]	1.89 ± 3.52	1.23 ± 2.81
Gamma[d]	0.61 ± 0.49	0.79 ± 0.71
Correlation	0.994 ± 0.009	0.973 ± 0.076

[a] Data are presented as the mean ± SD.
[b] Plasma concentration that produces pain relief 50% of maximum.
[c] First-order transfer rate constant of plasma between plasma and effector site.
[d] A constant that determines the steepness of the concentration-effect response profile.

These mean values indicate that; 1) doses were only slightly greater for Kapanol® than for MS Contin® (see Table 7), 2) concentrations at which the effect is half-maximal (EC_{50} values) were less for Kapanol® than for MS Contin® which could mean the lower fluctuation index achieves the same pain relief at a lower plasma morphine concentration, 3) the rate constant for transfer to the effect site (K_{eo}) was slightly greater for Kapanol® ($t_{1/2}$ = 22 min) than for MS Contin® ($t_{1/2}$ = 34 min) implying that the onset of pain relief would be faster for Kapanol®, and 4) gamma values were comparable and near unity which should be the case for a single, fast-acting narcotic agent, morphine.

Included in the analyses of plasma morphine concentrations were plasma concentrations of M-6-G to determine if there was an improvement in the fits compared to using plasma morphine concentrations alone. In general, the fits were not improved with the addition of the M-6-G plasma concentrations.

These results, in conjunction with the results from the primary efficacy parameters, indicate that the two treatment groups are statistically and clinically indistinguishable.

All of the efficacy data collected in the present study indicate that, at steady state, the two dosage formulations are statistically and clinically indistinguishable.

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3. Design, Results and Analysis of Supportive Controlled Trials

Three additional controlled studies were conducted comparing Kapanol®/Kadian™ Capsules to either IRM solution (Study MOBES-8/90), MS Contin® (Study MOR-2/92), or both (MOB-1/90). Study MOR-2/92 was a failed study due to poor study conduct and was terminated early for reasons discussed below. The three studies are summarized below.

a. Study MOBES-8/90 **NDA Volume 86**

Study MOBES-8/90 was a randomized, double-blind, double-dummy crossover study comparing the efficacy and safety of Kapanol® q12h to IRM solution q4h in the management of patients with moderate to severe cancer pain during the two 7 ± 1 day treatment arms of the crossover period. The crossover period was followed by a 12-week open-label assessment of the safety of Kapanol® q12h. The goal was for 24 evaluable patients to complete the study.

Prior to the beginning of the double-blind treatment period, a Lead-In Period of 3 to 14 days was included to titrate each patient to a stable dose of IRM solution. At the end of the Lead-In Period, qualified patients were randomly assigned to one of the two treatment groups before entering the Crossover Period. For the Crossover Period, a double-blind, double-dummy dispensing system was utilized to dispense blinded total daily doses of active study medications equivalent to the final total daily dose of IRM solution required to control pain during the Lead-In Period. During the first 12 hours after transferring from Lead-In to randomized treatment (Study Day 1) patients completed hourly pain scales (*i.e.,* VAS and VRS) for 12 hours following administration of the first dose at 1000h. On crossover Days 7 and 14, the patients were admitted to the hospital and again recorded hourly pain scales for 12 hours following administration of the 1000h dose.

In addition to the study medication dispensed, all patients also received rescue medication in the form of IRM solution to be taken in the event of breakthrough pain.

The primary efficacy parameters for the crossover study were:

- the patient's hourly scoring of pain intensity (VAS and VRS) from 1000h to 2200h on Days 7 and 14 in the hospital, i.e., pain intensity at steady-state for treatment with both IRM solution q4h and Kapanol® q12h;

- the patient's daily scoring of pain intensity (VRS) on Diary Cards before retiring each night; and

- the patient's hourly scoring of pain intensity (VAS and VRS) from 1000h to 2200h on Days 1 and 8, i.e., pain intensity during the day of transition from one formulation to the next in sequence.

The secondary efficacy parameters for the crossover study were:

- total daily use of rescue medication as recorded in the CRF;
- quality of sleep and disturbance of sleep by pain recorded on the Diary Card on waking each morning;
- the assessment of the investigator of the patient's pain control at each clinic visit;
- ECOG performance status; and
- cause-specific withdrawal rates.

The efficacy parameters for the follow-up study were:

- the patient's weekly scoring of their pain intensity (VRS) in the Diary;
- the patient's weekly assessment of their quality of sleep in the Diary; and
- the investigator's assessment of the patient's pain control at each clinic visit.

Thirty-six patients with chronic cancer pain were recruited. Nine patients withdrew before randomization; two of the patients were withdrawn at their own request, two because of poor pain control in the Lead-In Period and one each because of patient confusion, the need for radiotherapy, a low morphine-dose requirement, deterioration of the disease state, and a requirement for parenteral morphine.

Twenty-four of the 27 patients who commenced the crossover study completed both phases. Three patients were withdrawn; one of these patients was withdrawn in Phase 1 due to unacceptable side effects, another was withdrawn in Phase 2 due to a deteriorating disease state, and a third due to unacceptable side effects. In all cases the code envelopes were not opened.

Twenty patients were entered into the 12-week open-label phase of the study. A total of ten patients completed the 12-week follow-up study.

The morphine requirements for all patients during the Lead-In and Crossover Phases are summarized in Table 14 below. Morphine requirements were approximately log-normally distributed so that the geometric mean, presented below in addition to the arithmetic mean, more closely represents the average daily requirement for morphine.

TABLE 14
Morphine Dose (mg/day) during Lead-In and Crossover Phases
(Study MOBES-8/90)

Dose (mg/day)	At Start of Lead-In Phase (n = 36)	At End of Lead-In Phase (n = 33)	At Crossover (n = 27)
20 - 40	9	8	8
41 - 89	5	4	4
90 - 119	4	3	1
120 - 139	5	5	4
140 - 159	3	4	3
160 - 199	4	3	4
200 - 600	3	3	2
601 - 1400	2	2	0
1401 - 1500	1	1	1
Mean ± SD	209.9 ± 322.4	221.3 ± 351.8	170.0 ± 283.9
Median	105.0	120	120.0
Geometric Mean	113.3	116.7	103.5

In general, patients with a morphine demand less than 120 mg/day have only a limited tolerance to opioids and limited sensitivity to changes in daily morphine dose. Patients with a morphine requirement of 120 - 240 mg/day are both tolerant and moderately sensitive to both under-analgesia and withdrawal, while patients requiring more than 240 mg/day of morphine are highly tolerant and very sensitive to withdrawal if a non-equivalent dose of morphine is given. These relationships are an important indicator of possible under dosage from the Kapanol® formulation. In this study, about half of the patients had a lower morphine requirement, 1/3 had an intermediate demand, and 1/6 had a high morphine requirement. The average daily dose requirement based on the geometric mean changed very little between the beginning of the Lead-In Phase and the time of crossover.

During the follow-up phase, the morphine dose was adjusted as required. Average morphine requirements during this phase of the study are summarized in Table 15.

TABLE 15
Daily Morphine Dose (mg/day) during the Open-Label Extension Phase
(Study MOBES-8/90)

	Week of Follow-up						
	0 (n = 20)	2 (n = 20)	4 (n = 19)	6 (n = 15)	8 (n = 14)	10 (n = 14)	12 (n = 10)
Mean	175.0	178.0	192.2	137.1	148.6	150.0	110.0
Standard Deviation	317.5	318.4	313.3	116.1	143.3	142.7	54.4
Median	110.0	110.0	120.0	120.0	120.0	120.0	110.0
Geometric Mean	102.5	103.2	111.7	107.8	111.3	113.3	96.1

Although the mean morphine requirement varied considerably during the open-label phase, the average daily requirement expressed as the geometric mean showed much less variability. The results are also affected by the number of withdrawals discussed above.

The Day 7 steady state VAS and VRS score data for both treatment groups derived by combining data from each for the two treatment arms are presented in Table 16. A preliminary analysis showed that there were no statistically significant differences between treatments and no carry-over effects for either efficacy parameter; however, for VAS MIN there was a significant period effect. As with the data on daily morphine requirements, the geometric mean has been used to compare AUC across treatments for VAS scores because the AUC data were highly skewed.

TABLE 16
Steady-State VAS and VRS Scores on Day 7 for Each Treatment Group
(Study MOBES-8/90)

	Kapanol® Phase (n = 22)[a]			Morphine Solution Phase (n = 22)		
	AUC (mm/hr)[b]	MIN (mm)	MAX (mm)	AUC (mm/hr)	MIN (mm)	MAX (mm)
VAS Scores						
Mean ± SD	143.6 ± 159.1	7.3 ± 9.7	23.6 ± 23.8	141.7 ± 138.7	6.4 ± 8.9	**22.5 ± 20.4**
Median	69.1	2.5	17.5	114.6	3.0	**16.5**
Geom. Mean	74.7			68.2		
	Mean	MIN	MAX	Mean	MIN	MAX
VRS Scores						
Mean ± SD	0.92 ± 0.70	0.6 ± 0.6	1.5 ± 1.0	0.85 ± 0.68	0.6 ± 0.6	**1.3 ± 1.0**
Median	1.00	1	1	1.00	1	**1**

a Two patients (71 and 72) did not have 12 hour VAS and VRS scores on Day 7.
b AUC was calculated by the trapezoidal rule using the VAS scores as a function of time.

None of the differences between the paired scores for patients on Kapanol® q12h and IRM solution q4h were statistically significant, which suggests that the patients' experiences on Kapanol® and on morphine solution were clinically indistinguishable. This conclusion is supported by data on VAS scores at each of the hourly measurement periods on Day 7 of treatment which are presented graphically in Figure 4 for both treatment groups.

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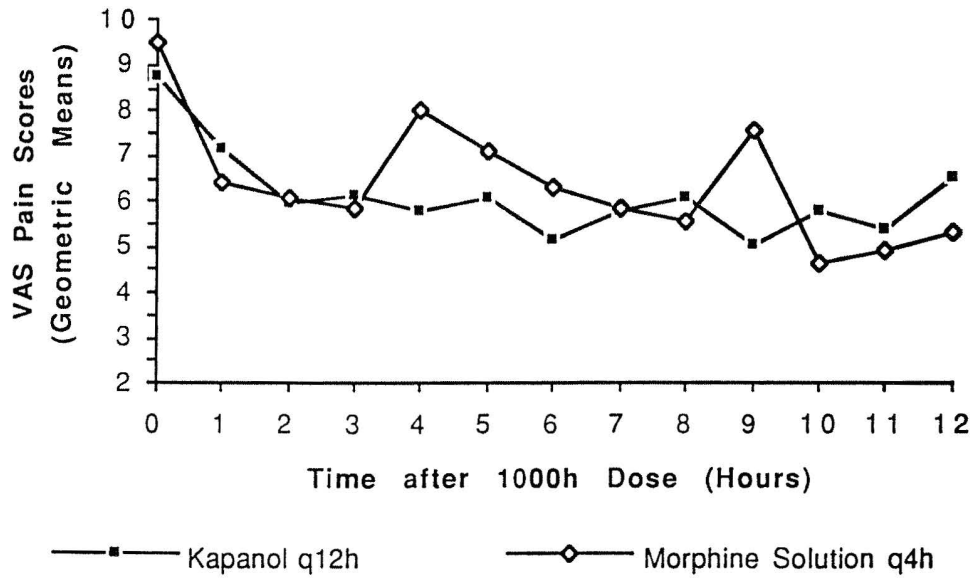
FIGURE 4. Steady-State VAS Pain Scores on Day 7 of Treatment (Study MOBES-8/90)



The data suggest that the pain scores are highest at 1000h just prior to the first daily dose, fall steadily until about 2 hours after the dose, and then plateau for 9 to 10 hours, particularly for the Kapanol® q12h treatment group. The morphine solution scores tended to rise at the end of the first and second dosing intervals shown (3-4 and 8-9 hours) and then decrease again following re-dosing. It should be remembered that a clinically significant difference in pain scores is considered to be 3 to 4 mm on the VAS and that the scale employed had a maximum value of 100; the geometric mean values reported are clustered over a range of only a few millimeters at the bottom end of the scale indicating no clinical difference between the two equally effective treatments.

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This conclusion that the two treatments are virtually indistinguishable clinically is supported by the secondary efficacy parameters presented in Table 17.

TABLE 17
Secondary Steady-State Efficacy Parameters During Crossover Period (n = 24)
(Study MOBES-8/90)[a]

Parameter	Kapanol®	Morphine Sol.
Rescue Medication		
Total Doses in 1 Week	104	85
Doses per Patient (Mean ± SD)	4.3 ± 5.2	3.5 ± 4.5
Day 1 of Treatment		
No. of Patients Taking	5	4
No. of Doses Taken	7	4
Day 7 of Treatment		
No. of Patients Taking	5	5
No. of Doses Taken	8	10
Quality of Sleep[b] (Mean ± SD)	1.99 ± 0.57	1.95 ± 0.49
Proportion of Night's Sleep Disturbed (Mean ± SD)	0.33 ± 0.34	0.30 ± 0.37

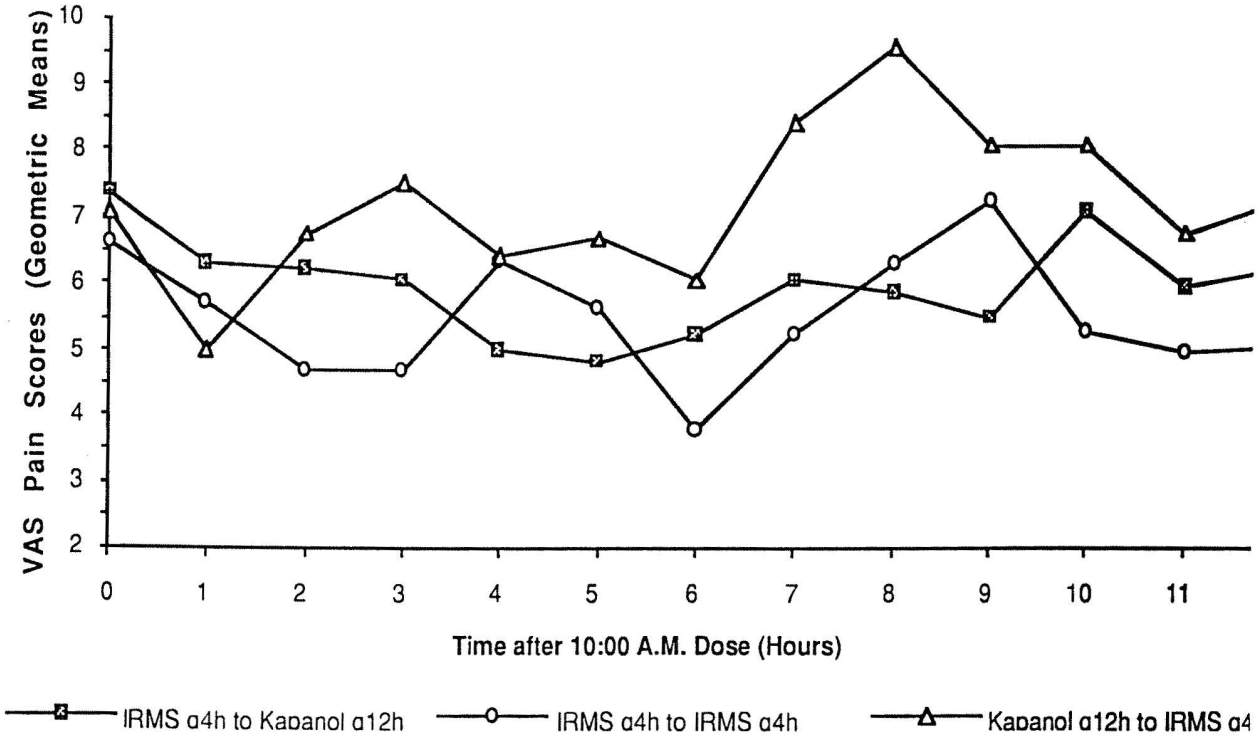
a Evaluations of rescue doses taken on Days 1 and 7 were assessed following the taking of the dose at 1000h and continued for 12 hours.

b Based on a scale from 1 to 4 with 1 representing "slept very well", 2 representing "slept quite well", 3 representing "slept poorly" and 4 representing "slept not at all".

None of the observed comparisons were statistically significantly different. In addition, the investigator's assessments of pain control showed that for both treatments, the ratings were all either "complete" or "acceptable" for both treatments. Likewise, there were no significant differences in Eastern Cooperative Oncology Group (ECOG) performance status or cause specific withdrawals in the number of patients, study phase, or treatment at the time of withdrawal. These results confirm the conclusion drawn above that the two treatments are clinically indistinguishable.

Another of the objectives was to examine pain control on the day of transfer to Kapanol® treatment and also from Kapanol® back to the Lead-In medication, IRM solution. Pain control in the former comparison was of interest because Kapanol® is a sustained-release formulation of morphine, in which plasma morphine concentrations after a single oral dose rise more slowly than with IRM solution, potentially exposing the Kapanol® treated patients to perceived under-dosing on the transition day. Because of the cross-over design, there were three distinct groups on the transition days; the first dose of Kapanol® following IRM solution after either the Lead-In Period or after treatment in the first study arm with IRM solution; a continuation of IRM solution from the Lead-In Period; and the transition to IRM solution from Kapanol®. The results for all three treatments during the transition days are presented in Figure 5.

FIGURE 5. Comparison of VAS Pain Scores on Treatment Transition Days (Study MOBES-8/90)



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As at steady state on Day 7, there was a minor peak in pain scores at the 10:00 A.M. dosing period. There was some evidence of a 4-hour periodicity for patients receiving solution, whether following Kapanol® or not. Similar to the results on Day 7, on the first day of Kapanol® treatment, pain scores decreased gradually during the first 4 hours after treatment. If the sustained-release nature of the Kapanol® capsule had resulted in the perception of under-dosing on the part of the patients it would be expected that the pain scores would rise in the hours following the transition to this dosage form; however, this was not the case. As with the steady-state data on Day 7, pain control scores throughout the 12-hour observation period for all treatment groups were clustered within a few millimeters of each other at the bottom end of the 100 mm scale, indicating little pain in any of the treatment groups and no clinically significant differences among any of the treatment groups.

Patients continuing into the open-label Kapanol® q12h phase of the study continued to experience good pain control.

Conclusions to be drawn from the efficacy results of this randomized, double-blind, double-dummy study are summarized below:

- at steady state, sustained-release Kadian™ Capsules administered every 12 hours are as effective for controlling cancer pain as IRM solution administered every four hours;
- good pain control is maintained on the first day of transfer from IRM solution to Kadian™ Capsules; and
- Kadian™ Capsules are efficacious during long-term use.

b. Study MOR-2/92 **NDA Volume 76**

Study MOR-2/92 was a randomized, double-blind, double-dummy balanced incomplete block design crossover study comparing the pharmacokinetics and pharmacodynamics of Kapanol® administered q24h and q12h to MS Contin® q12h in the management of patients with moderate to severe chronic pain during the two 7-day treatment arms of the crossover. In contrast to most of the other controlled studies, patients in the present study were outpatients throughout and were not hospitalized during the critical evaluation days for safety and efficacy.

Eighteen patients with moderate to severe pain were randomized and received study medication. Two patients were discontinued prematurely, one for non-compliance and one at the patient's own request. Ten patients completed the study but violated the protocol; six patients for non-compliance, three patients because of ineligibility, and one patient because of increasing rescue medication requirements. Only 6 patients completed the study according to the protocol.

In conclusion, this was not an adequately controlled study and the study was terminated prematurely. For these reasons, no conclusions related to the study efficacy objectives could be drawn. All safety data has been fully reported in the Final Study Report as well as in the Integrated Summary of Safety.

c. Study MOB-1/90 **NDA Volume 27**

Study MOB-1/90 was a randomized, open-label, three-way crossover trial comparing the steady-state pharmacokinetics of oral IRM solution q4h, Kapanol® capsules q12h, and MST Continus® q12h. Patients selected to participate in this study were experiencing moderate to severe stable pain due to cancer. Note: MST Continus® is the trade name under which MS Contin® is marketed in the Australia and Europe by Napp Laboratories.

The objectives of the study were:

a. to compare the steady-state pharmacokinetics of the identical daily dose of morphine given as IRM solution every four hours with MST Continus® tablets and Kapanol® capsules given every 12 hours;

b. to examine the steady-state concentrations of morphine, morphine-3-glucuronide, and morphine-6-glucuronide in plasma in at least six of the 24 evaluable patients.

Eligible patients initially received the morphine solution every four hours for at least 8 days during a Lead-In Period. The dosage level was adjusted to provide control of pain and remained at a constant level for the last three days of this period.

During the crossover period all patients received, in a randomized crossover fashion, Kapanol® capsules q12h, MST Continus® tablets q12h, and IRM solution q4h for 7 days. The total daily dose administered during the crossover period was the same as that which provided adequate pain relief during the last three days of the Lead-In Period.

A blood sample was collected once during the Lead-In Period. To determine whether steady-state had been achieved, pre-dose samples were collected on Days 6, 13, or 20 from patients receiving MST Continus® tablets or Kapanol® capsules; and on Days 7, 14, or 21 from patients receiving the solution. Serial blood samples were collected over a 12-hour period following administration of the 1000h dose on Days 7, 14, and 21.

During the Lead-In Period, the patient evaluated pain control of the IRM solution on a daily Diary Card by scoring pain on a 100 mm VAS scale, where 0 represented no pain and 100 represented worst possible pain imaginable, prior to each dosing time. In addition, the times and doses of administration of IRM solution and the use of rescue analgesia were recorded daily by the patients in their diaries. At the end of the Lead-In Period, when the patients returned to the clinic to be randomized to the crossover phase, an assessment of pain control over the last three days of the period was recorded on the CRF using the VRS.

During the crossover periods the patients completed pain control assessments daily on Diary Cards using the 100 mm VAS scale described above. On Days 7, 14, and 21, the days on which blood samples were collected for the pharmacokinetic analyses, pain control (patient's opinion) and general well-being (patient's opinion) were recorded by the study nurse using a VRS before the patient retired for the night.

Fifty (50) patients with moderate to severe cancer pain entered this study. Thirty-six (36) of the patients were male and fourteen (14) were female. The population ranged in age from 39 to 85 years (mean, 65 years) and weighed an average of 66 kg (range, 44 - 110 kg). Of the 50 patients who entered the Lead-In, 16 withdrew from the study for a variety of reasons, including: inadequate pain relief (2); noncompliance with the study protocol (4); need for chemotherapy or radiotherapy (2); laboratory abnormalities (2); low morphine requirement (3); unacceptable side effects (2); and at the patient's request (1). Thirty-four (34) patients were randomized.

Twenty-four (24) of the 34 patients who were randomized to treatment completed the trial. Only one of the discontinuations was due to an adverse experience. The other nine withdrawals were for reasons unrelated to treatment with the study medication, including: deteriorating clinical condition (5); inability to draw blood (2); noncompliance with the protocol (1); and at the patient's request (1). Four (4) patients withdrew while receiving the solution, three (3) while receiving MST Continus® tablets, and three (3) while receiving Kapanol® capsules.

The morphine dosage, fixed during the Lead-In period, ranged from 40 to 320 mg daily (mean, 142.5 mg/day; median, 120 mg/day) among the 24 patients who completed the trial. The majority of these patients (n = 14) received doses ranging from 100 to 180 mg/day; five patients received lower doses (40 or 80 mg/day) and five patients received higher doses (200 to 320 mg/day).

The two efficacy parameters measured at steady state before patients retired for the evening on Day 7 of each treatment sequence were pain control and well-being. The results are reported in Table 18.

TABLE 18
Efficacy Results on Final Day of Each Crossover Period (Study MOB-1/90)

Efficacy Parameter	Kapanol® q12h	IRM q4h	MST Continus® q12h
n =	24	24	24
Pain Control (a)	1.2 ± 0.6	1.2 ± 0.5	1.2 ± 0.5
Well-Being (b)	1.0 ± 1.0	1.1 ± 0.8	1.1 ± 0.7

Data are presented as the mean ± SD.
(a) Pain control scale: 0=complete; 1=partial, acceptable; 2=partial, unacceptable; 3=no pain control.
(b) Well-being scale: 0=good; 1=satisfactory; 2=poor; 3=very ill.

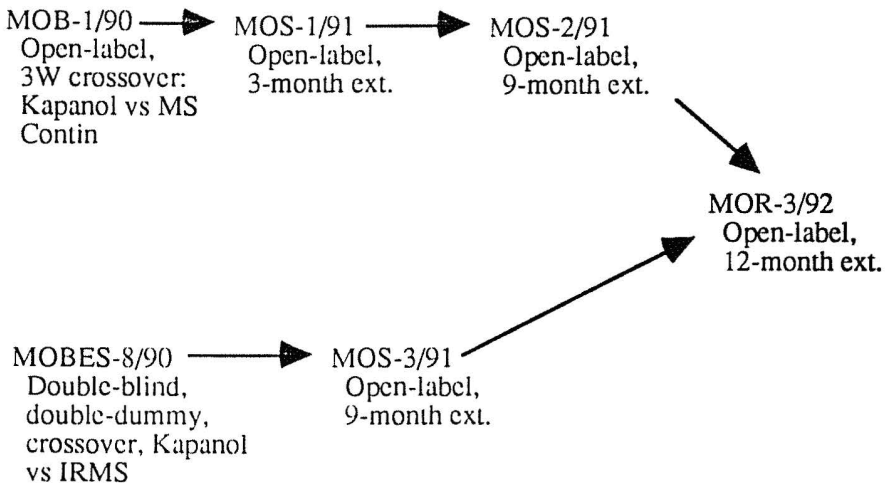
The efficacy data indicate that there were no differences between any of the treatment groups when measured at steady-state on Day 7 of each of the crossover arms.

Prior to discharge, patients were given the option to continue taking Kapanol® capsules every 12 hours as part of an open-label follow-up or extension study (Study MOS-1/91).

4. Design, Results, and Analysis of Uncontrolled Trials

In addition to the five controlled studies described above, five open-label extension studies were conducted to study the safety and efficacy of Kadian™. Four of the open-label studies (MOS-1/91, MOS-2/91, MOS-3/91, and MOR-3/92) originated as extensions of previously completed studies. The relationships between these open-label extension studies and their predecessors are depicted in Figure 6.

FIGURE 6. Relationships Between Open-Label Extension Studies



The other open-label study was MOR-5/92. Because Study MOB-1/90 was a crossover design, it was considered to be a controlled study.

a. Study MOS-1/91 **NDA Volume 88**

Study MOS-1/91 was a single-center, open-label, 12-week efficacy and safety evaluation which followed the open-label, randomized pharmacokinetic crossover study MOB-1/90 described above.

Patients were recruited from the previous study and continued on the same 12-hourly dose of Kapanol® they received during the 21-day crossover period. Dosage adjustments of Kapanol® capsules were, however, permitted during the study. Rescue medication was permitted if, in the opinion of the investigator, it was required by the patient. The rescue medication was dextromoramide tartrate 5 mg tablets (Palfium®, Faulding Pharmaceuticals). All patients returned to the clinic at weeks 2, 4, 6, 8, 10, and 12. During these visits, the investigator performed a physical examination and made an assessment of the patient's vital signs, pain control and side-effects. Laboratory tests were performed every 4 weeks.

Nineteen patients aged 18 years and over with moderate to severe chronic pain resulting from disseminated locally invasive cancer and who had completed Study MOB-1/90 entered the study. Nine patients successfully completed the study. Five patients were withdrawn because of disease progression, two patients died as a result of disease progression, one patient was unable to attend clinic visits and two patients withdrew at their own request. All 19 patients who commenced the study were included in the descriptive analysis of pain control, adverse events, and safety assessments.

Patients were instructed to rate the following parameters on their Diary Card once each week using a VRS:

- quality of sleep (on waking each morning),
- disturbance of sleep by pain (and severity if disturbed),
- adverse events (before retiring each night; degree of nausea and vomiting, movement of bowels, sleepiness, anxiety, and appetite), and
- overall pain intensity (before retiring each night).

The study began with 14 males and 5 females with widely varying morphine demand. The morphine requirements throughout the follow-up period are presented in Table 19.

On completion of the study, patients were able to continue open-label treatment with Kapanol® capsules in a nine month extension study (Study MOS-2/91) or receive alternative treatment at the investigator's discretion.

TABLE 19
Analysis of Morphine Dose (mg/day) During Open-Label Follow-Up Period (MOS-1/91)

Dose Range	Week of Follow-Up						
	0	2	4	6	8	10	12
20 - 40	2	2	2	1	0	0	0
41 - 89	2	2	2	2	2	3	0
90 - 119	2	2	2	2	1	1	0
120 - 139	4	2	0	1	1	0	1
140 - 159	3	2	2	2	1	2	1
160 - 199	1	2	1	1	1	1	1
200 - 399	4	4	6	5	7	6	4
400 - 600	1	2	2	2	2	2	2
Total Patients	19	18	17	16	15	15	9
Note that the dose ranges are not equal.							
Mean	151.6	164.4	192.9	190.0	232.0	238.0	295.6
SD.	91.5	105.1	129.4	127.3	150.0	173.9	149.6
Range	40 - 400	40 - 400	40 - 500	40 - 500	60 - 600	50 - 600	120 - 600

In this study, about one half of the patients began with a low morphine demand, one third had an intermediate demand and one sixth had a high morphine demand. By week 12, only about one tenth of patients had a low morphine demand, one fifth had an intermediate demand and two thirds had a high morphine demand.

The periodic dose increases over time were required by most patients to maintain adequate analgesia. This would be expected because of the combined effects of disease progression. There was no evidence of a trend towards a failure of adequate pain control from Kapanol® capsules administered every 12 hours.

The summary of patient diary VRS data on severity of pain during each of the follow-up weeks is presented in Table 20 below:

TABLE 20
Weekly Summary of Patient Diary Data on Severity of Pain During the Open-Label Extension Period (Study MOS-1/91)

	Week of Follow-up											
Category	1	2	3	4	5	6	7	8	9	10	11	12
Number of Patients	19	18	18	17	16	16	16	15	15	15	12	9
Severity of Pain												
0 = No pain	2	2	0	0	1	2	3	3	3	3	2	1
1 = Mild	3	3	4	5	5	2	1	2	1	0	1	1
2 = Moderate	7	8	10	8	3	2	5	2	4	4	2	2
3 = Severe	1	1	1	2	4	5	2	3	1	1	1	1
4 = Intolerable	0	0	0	0	0	0	0	0	1	0	0	0
Data not recorded	6	4	3	2	3	5	5	5	5	7	6	4

The averages over individual patient diaries ranged from 0.2 to 3.0, with an overall mean of 1.72 (SD = 0.71). This corresponded to mild to moderate pain on average. There was no evidence of a loss of pain control with time.

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Below is the summary of patient diary data on quality of sleep during each week of the treatment period:

TABLE 21
Weekly Summary of Patient Diary Data on Quality of Sleep During the Open-Label Extension Period (MOS-1/91)

	Week of Follow-up											
Category	1	2	3	4	5	6	7	8	9	10	11	12
Number of Patients	19	18	18	17	16	16	16	15	15	15	12	9
Quality of Sleep												
0 = Slept very well	6	2	3	3	3	2	4	1	3	2	1	1
1 = Slept quite well	4	10	7	9	7	7	6	9	6	5	4	3
2 = Slept poorly	4	2	4	4	4	3	2	2	2	2	1	2
3 = Did not sleep at all	0	0	0	0	0	0	0	0	0	0	0	0
Data not recorded	5	4	4	1	2	4	4	3	4	6	6	3
Sleep disturbed by pain												
Yes	6	5	6	8	7	8	6	6	5	4	2	3
No	8	9	9	8	7	4	6	5	6	5	4	3
Data not recorded	5	4	3	1	2	4	4	4	4	6	6	3

The average quality of sleep ratings ranged between 0 and 2, with an overall mean of 0.99 (SD 0.59), corresponding to a generally acceptable level of sleep quality.

No comparative analysis or significance testing was performed on these data.

Additional analyses on the investigator's assessments of pain control were undertaken in which the average rating on each scale, over visits for which valid data were available, was obtained for each patient. These data are presented in Table 22.

TABLE 22
Frequency Counts of Investigators' Assessments of Pain Control During the 12-Week Open-Label Follow-up Period (Study MOS-1/91)

	Week of Follow-Up					
Category	2	4	6	8	10	12
Number of Patients	18	17	16	15	15	9
Pain Control						
0=Complete	0	1	1	2	1	1
1=Partial, acceptable	10	11	6	8	6	5
2=Partial, unacceptable	6	4	7	4	4	3
3=No pain control	0	0	1	1	0	0
Data not recorded	2	1	1	0	4	0

The majority of patients had partial, acceptable pain control. The averages over individual patient pain control ratings ranged from 0.67 to 2.50, with 14 of the 18 evaluable patients having average ratings between 1 and 2. The overall mean was 1.3 (SD = 0.45), which suggested that although seldom pain-free, patients' pain was acceptably controlled with Kapanol® q12h.

The use of Palfium® (dextromoramide tartrate 5 mg) tablets as rescue analgesia is documented in Table 23 below:

TABLE 23
Total Number of Rescue Medication Tablets Taken During 2-Week Periods of the Open-Label Follow-Up Study (Study MOS-1/91)

	Weeks of Follow-Up					
No. of Tablets	1 & 2 (n = 18)	3 & 4 (n = 17)	5 & 6 (n = 16)	7 & 8 (n = 16)	9 & 10 (n = 14)	11 & 12 (n = 8)
Min.	0	0	0	0	0	0
Max.	28	38	40	43	75	38
Total	162	202	180	206.5	213	131.5
Mean	9.0	11.9	11.3	12.9	15.2	16.4
Std. Dev.	7.8	10.6	11.0	12.7	19.4	15.4

Usage varied widely between patients, ranging from 0 to 75 tablets per patient over a 2 week period, but was relatively stable for each individual patient.

The data presented above indicate that from both the patient's and investigator's perspective, pain was acceptably controlled with no loss of pain control with time. In addition, patients indicated they had received a generally acceptable level of sleep quality.

b. Studies MOS-2/91 and MOS-3/91 **NDA Volume 89**

These studies entered 29 patients into 9-month open-label extension studies of Kapanol® q12h in patients with chronic cancer pain who had previously participated in one of the earlier Kapanol® studies (Studies MOB-1/90, MOS-1/91 or MOBES-8/90, see Figure 6 for relationships between these studies). Seven (7) of these patients went on to enroll in the 12-month study MOR-3/92 described in the following section. One of the 9 month studies was a single center study (Study MOS-2/91), the other 9 month study (Study MOS-3/91) was conducted at three centers. These two protocols were identical except for a different rescue medication being specified.

All patients received open-label Kapanol® 12 hourly. The dose was determined by previous morphine requirements and dosage increases were permitted at any time throughout the study. Rescue medication was also allowed as required; dextromoramide tablets given orally were used in Study MOS-2/91, IRM solution was used in Study MOS-3/91.

Patients were treated primarily on an out-patient basis, attending clinic visits monthly during the 9-month studies. At each clinic visit, patients were seen by the investigator who performed a physical examination, assessed pain control, morphine-related side-effects and adverse events. Changes in medication and use of rescue analgesia were also recorded. In addition, blood and urine samples were obtained at each visit for routine laboratory tests. Patients were contacted regularly by telephone between clinic visits to assess pain control and adverse events.

Eight patients completed the 9-month studies. Of the 21 patients who withdrew, 12 withdrew due to disease state deterioration; several of these patients died within a few days of withdrawal. Four patients were withdrawn as a result of death due to disease progression. Two patients were withdrawn at their own request, another patient because they were unable to attend the clinic visits, another due to unacceptable side-effects, and one patient was withdrawn because of inappropriate use of rescue morphine.

Ten deaths were reported during the 9-month studies. None of these were related to Kapanol®. All patients enrolled in these studies were included in the descriptive analysis of pain control, side-effects and safety assessments.

The primary efficacy parameter for these studies was the investigator's assessment of the patient's pain control at each clinic visit.

Twenty-four men and five women entered the two studies. The mean age was 64.6 years with a standard deviation of 10.7 years. They exhibited a wide range of morphine requirements. A frequency distribution of these requirements is presented below in Table 24.

TABLE 24
Analysis of Morphine Dose (mg/day) During the Two 9-Month Open-Label Extension Studies (Studies MOS-2/91 & MOS-3/91)

Dose Range	Month of Follow-Up 0	1	2	3	4	5	6	7	8	9
20 - 40	4	4	3	2	1	1	0	0	0	0
41 - 89	3	3	3	3	3	1	1	1	1	1
90 - 119	2	2	0	1	1	1	0	0	0	0
120 - 139	3	3	2	1	1	2	2	2	1	1
140 - 159	4	3	4	1	1	1	1	1	2	1
160 - 199	4	4	2	3	2	1	2	2	1	1
200 - 399	5	6	8	8	8	6	5	4	3	2
400 - 599	3	2	1	1	1	3	2	1	2	2
600 - 1100	1	1	2	2	0	0	1	1	0	0
Note that the dose ranges are not equal.										
No. of Patients	29	28	25	22	18	16	14	12	10	8
Mean	185.5	185.4	217.6	250.0	195.6	212.5	248.6	236.7	220.0	240.0
SD	144.1	164.6	209.5	249.5	106.0	115.9	144.6	148.9	116.2	126.5
Range	40 - 600	20 - 800	40 - 900	40 - 1100	40 - 400	40 - 400	60 - 600	60 - 600	60 - 400	80 - 400

During the 9 month studies, there was a trend for the dose of morphine required for pain control observed from both the mean data and from the monthly frequency distributions to increase with time as the underlying disease state progressed.

The frequency counts of investigator's assessments of pain control utilizing the VRS Scale during the studies is presented in Table 25 below:

TABLE 25
Frequency Counts of Investigator's Assessments of Pain Control During the Two 9-Month Open-Label Extension Studies (Studies MOS-2/91 & MOS-3/91)

	Month of Follow-up								
Category	1	2	3	4	5	6	7	8	9
Number of Patients	28	25	22	18	16	14	12	10	8
Pain Control									
0 = Complete	3	4	3	2	2	2	1	1	1
1 = Partial, acceptable	17	17	14	14	8	7	9	5	4
2 = Partial, unacceptable	6	2	3	0	4	3	1	4	3
3 = No pain control	0	0	0	1	1	0	0	0	0
% with at least Partial, Acceptable Pain Control	71	84	77	89	63	64	83	60	63
Data not recorded	2	2	2	1	1	2	1	0	0

In general, the majority had partial, acceptable pain control. Twenty-one of the 29 evaluable patients in the 9-month studies had average ratings between one and two. The overall mean was 1.1 (SD = 0.5). Over the duration of the study, 60 to 89% of the patients (average = 72%) experienced acceptable pain control as assessed by the investigator. This compared to 87% and 95% for Kapanol® q12h and Kapanol® q24h on the Final Day (Day 7) of the blinded portion of Study CDD-14556.

These results suggest that although patients may not have always been totally pain-free, their pain was acceptably controlled with Kapanol®.

Only the total usage of rescue analgesia between clinic visits was recorded. Tables 26 and 27 below provide summary information on rescue medications in Studies MOS 2/91 and MOS-3/91, respectively. Since the two studies utilized different rescue medications, these are presented by study below.

TABLE 26
Rescue Analgesia, Dextromoramide Tablets 5 mg in Study MOS-2/91.
Total Number of Tablets Taken During 4-Week Periods
of the 9-Month Extension Study

	Month of Follow-Up								
	1	2	3	4	5	6	7	8	9
N	10	10	8	5	4	4	3	3	2
Min	0	0	2	3	4	2	3	6	18
Max	46	24	26	28	30	46	34	38	20
Total	107	118	97	73	64	91	67	77	38
Mean	10.7	11.8	12.1	14.6	16.0	22.8	22.3	25.7	19.0
SD	14.2	9.1	10.1	9.7	11.2	18.6	16.9	17.2	1.4

TABLE 27
Rescue Analgesia, Morphine Hydrochloride Solution 5 mg/mL in
Study MOS-3/91.
Total Volume (mL) Used During 4-Week Periods
of the 9-Month Extension Study

	Month of Follow-Up								
	1	2	3	4	5	6	7	8	9
N	15	13	13	11	9	9	8	5	4
Min	0	0	0	0	0	0	0	0	0
Max	450	540	395	685	250	450	455	455	300
Total	1794	1798	1992	1675	775	882	1100	1126	596
Mean	119.6	138.3	153.2	152.3	86.1	98.0	137.5	225.2	149.0
SD	128.5	162.2	134.9	196.4	90.8	150.1	154.4	161.0	122.7

During the Open-For most patients, rescue usage was relatively stable; the regular review of their basic daily morphine requirements enabled the maintenance of adequate pain control. Changes in the means were heavily influenced by withdrawals from the study.

In conclusion, pain control throughout the 9-month open-label extension period continued to be acceptable with some patients requiring occasional doses of rescue medication.

c. Study MOR-3/92 **NDA Volume 89**

Seven of the eight patients who completed the 9-month studies, MOS-2/91 and MOS-3/91, went on to enroll in the present study which was 12 months in duration. As with the 9-month studies, the present 12-month study was also a multicenter study conducted at two of the four original centers.

All patients received open-label Kapanol® capsules every 12 hours. The dose was determined by previous morphine requirements and dosage increases were permitted at any time throughout the study. Rescue medication was also allowed as required; in contrast to studies MOS-2/91 and MOS-3/91, the type of rescue medication to be utilized was unspecified in the present study.

Patients were treated primarily on an out-patient basis, attending clinic visits every two months during the 12-month open-label study. At each clinic visit, patients were seen by the investigator who performed a physical examination and assessed pain control, morphine-related side-effects, and adverse events. Changes in medication and use of rescue analgesia were also recorded. In addition, blood and urine samples were obtained at each visit for routine laboratory tests. Patients were contacted regularly by telephone between clinic visits to assess pain control and adverse events.

In the present study, one of the seven patients completed the study; a further two patients continued taking Kapanol® on prescription after the study was terminated. Four patients were withdrawn: two due to disease state deterioration, one at the patient's request and one patient was withdrawn because of a morphine overdose. Subsequently, it was considered inadvisable for this patient to have access to supplies of morphine.

No deaths occurred in the present 12-month study. All patients enrolled in this study were included in the descriptive analysis of pain control, side-effects and safety assessments.

The primary efficacy parameter for this study was the investigator's assessment of the patient's pain control at each clinic visit.

Five men and two women entered the study. The mean age was 57.4 years with a standard deviation of 10.4 years. They exhibited a wide range of morphine requirements. A frequency distribution of these requirements is presented below in Table 28.

TABLE 28
Analysis of Morphine Dose (mg/day) Label
12-Month Extension Study (Study MOR-3/92)

	Month of Follow-Up						
Dose Range	0	2	4	6	8	10	12
0 - 20	0	0	0	1	0	0	0
21 - 99	1	1	1	1	1	1	0
100 - 199	2	2	2	1	1	0	0
200 - 299	0	0	0	0	0	0	0
300 - 399	2	0	0	0	0	1	1
400 - 499	2	2	1	1	1	0	0
500 - 600	0	0	1	1	1	1	0
Note that the dose ranges are not equal.							
Number of Patients	7	5	5	5	4	3	1
Mean	254.3	236.0	248.0	220.0	275.0	293.3	300.0
SD	129.5	153.9	190.1	217.3	206.8	210.1	-
Range	80 - 400	80 - 400	80 - 500	0 - 500	80 - 500	80 - 500	300 - 300

In the present 12-month study there was no strong trend for the dose to increase with time since the condition of several of the patients was stable, and one elected to cease morphine altogether after 6 months. All but one of the patients had a morphine requirement in excess of 100 mg/day; the remaining patients had morphine requirements in the range of 300 to 600 mg/day and would be expected to be very sensitive to under-analgesia. If such under-dosing occurred it should be reflected in the investigator's assessment of pain control.

Frequency counts of investigator's assessments of pain control utilizing a VRS pain scale during the study is presented in Table 29 below:

TABLE 29
Frequency Counts of Investigator's Assessments of Pain Control During the 12-Month Open-Label Extension Study (Study MOR-3/92)

	Month of Follow-up						
Category	0	2	4	6	8	10	12
Number of Patients	7	5	5	5	4	3	1
Pain Control							
0=Complete	1	1	1	1	2	0	0
1=Partial, acceptable	3	2	4	2	1	2	1
2=Partial, unacceptable	3	1	0	1	1	0	0
3=No pain control	0	1	0	1	0	0	0
% with Acceptable Control	57	60	100	60	75	67	100
Data not recorded	0	0	0	0	0	1	0

In general, the majority had partial acceptable pain control. The majority of patients had assessments of 0 and 1. The overall mean was 1.32 (SD = 0.72). These results indicated that the majority of patients did not appear to the investigator to be under-medicated. Overall, the percentage of patients with acceptable pain control, as assessed by the study investigator over the 12-month study period, was 74%. This compared to 72% reported in the 9-month extension studies MOS-2/91 and MOS-3/91. These results indicated that there was no dimunition in pain control over the 21 months covered by these long-term extension studies.

These results suggested that although patients may not have always been totally pain-free, their pain was acceptably controlled with Kapanol®.

Because the rescue medication for this study was not specified, different patients received different rescue medications. Thus it is not possible to summarize the need for rescue medication for the few patients involved in this study.

In conclusion, Kapanol® capsules given every 12 hours were safe and effective when administered over a period of up to 21 months.

d. Study MOR-5/92 **NDA Volume 92**

This was a multicenter, open-label, parallel group study to investigate pain control during transfer from IRM solution or MS Contin® tablets to Kapanol® capsules and from Kapanol® capsules to parenteral morphine in patients with moderate to severe cancer pain. During the course of the study none of the patients required transfer to parenteral morphine, thus this aspect of the trial does not receive further consideration in the discussion to follow.

The objective was to investigate if pain control was maintained or if the quality of sleep and the severity of side effects were altered when oral IRM solution q4h or oral MS Contin® q12h controlled-release morphine sulfate tablets were replaced with oral Kapanol® capsules administered either q12h or q24h for the treatment of moderate to severe chronic pain associated with cancer. Treatment with Kapanol® capsules for assessment of efficacy and safety was for a period of one week.

In addition, the peak and trough plasma morphine concentrations on the last day of the Lead-In Period were compared with the peak and trough plasma morphine levels following transfer to Kapanol® capsules. These plasma concentrations were obtained as follows:

- Last day of Lead-In Period at 0 hours (trough) and 0.5 hours (peak) after the first morphine dose for IRM solution patients and at 0 hours (trough) and 4 hours (peak) after the first dose for MS Contin® patients.

- First day of Kapanol® treatment period at 6 hours (peak) and at 24 hours (trough) after the first Kapanol® dose.

Prior to entry into the experimental phase of the study, patients completed a Lead-In Phase which lasted 3 - 14 days during which they were to achieve an effective stable daily dose on IRM solution q4h or MS Contin® tablets q12h. The dose of Kapanol® capsules was to be based on the total daily dose of IRM solution or MS Contin® tablets, plus rescue, which provided adequate pain control during the Lead-In Period. Dextromoramide 5 mg tablets (Palfium®, Faulding Pharmaceuticals) were available as rescue medication during the Lead-In Period and Treatment Periods as needed for all study patients.

The primary efficacy parameters during the transfer period from other opioids to Kapanol® were the times and doses of rescue medication over the 48-hour assessment period encompassing the last day of the Lead-In Period and the first day of the Kapanol® Treatment Period. The secondary efficacy parameters on the last day of the Lead-In Period and during the first day of Kapanol® treatment were periodic assessments of pain using a VAS (100 mm) and VRS (5-point for pain intensity and 4-point for pain control). Secondary efficacy measures during the course of Kapanol® were:

- Quality of sleep assessments on each morning of the Treatment Period.
- Pain intensity assessments, VRS, on each morning for days 2 - 7.
- Pain control assessments, VRS, on each evening of the Treatment Period.
- An investigator Global Assessment for the previous week on the last day of the Treatment Period.
- A Patient Treatment Preference on the last day of the Treatment Period.

A total of 50 evaluable patients were entered into the study. A total of 49 patients were enrolled in eight centers. Of these patients, eight withdrew during the Lead-In Period and were considered non-evaluable; 4 were withdrawn due to adverse events, 2 at their own request, 1 who was ineligible, and 1 who could not be stabilized. Of the eight patients who withdrew during the Lead-In Period, they were equally divided between those receiving IRM solution and those receiving MS Contin®. Forty-one patients were randomized to Kapanol®; four withdrew during the Treatment Period and an additional 3 patients were treated as though they had completed the study even though they stopped taking Kapanol® prior to the sixth day of the Kapanol® Treatment Period. These latter three patients were listed as completing the final period and elicited for their treatment preference. Of the seven patients who withdrew from the Kapanol® Treatment Period, 2 withdrew because of treatment failure (days 1 and 3 of treatment), 1 developed a confusional state and was unable to comply with the protocol (day 2), 1 withdrew at their own request because of side effects (day 4), and 3 provided no reason for withdrawal (one at day 1 and two at day 5) but were considered as having completed.

A total of 27 males and 14 females with evaluable data, equally divided between IRM solution and MS Contin®, with an average age of 63.4 years entered the Kapanol® treatment phase. All but two of the patients were Caucasian. The morphine requirements at the end of the Lead-In Period for patients receiving IRM solution was 119.8 ± 90.7 mg and for MS Contin® was 167.0 ± 146 mg; the difference between these two groups was not statistically significant ($p = 0.23$).

The proportion of patients who took rescue medication in both the Lead-In and Kapanol® Treatment Periods is presented in Table 30 below:

TABLE 30
Proportion of Patients Requiring Rescue Medication on the Last Day of the Lead-In Period and the First Day of Kapanol® Treatment (Study MOR-5/92)

	Last Day of Lead-In Period		First Day of Kapanol® Treatment	
	IRM	MS Contin®	q12h	q24h
No	15 (71%)	16 (80%)	11 (55%)	10 (48%)
Yes	6 (29%)	4 (20%)	9 (45%)	11 (52%)
Total	21	20	20	21

There were no statistically significant differences by Fisher's exact test between treatment groups on either the last day of the Lead-In period or the first day of Kapanol® treatment. On the first day of the Treatment Period, however, the proportion of patients who required rescue medication was about twice that in the Lead-In Period (29% and 20% for IRM solution and MS Contin® respectively during the Lead-In Period and 45% and 52% for Kapanol® q12h and Kapanol® q24h, respectively on the first day of the Treatment Period). The percentage of patients needing rescue medication on the first day of treatment is somewhat higher than in two other double-blind, double-dummy studies (Studies MOBES-8/90 and MOR-9/92). In study MOBES-8/90, 21% of patients receiving Kapanol® q12h and 17% of patients receiving IRM solution q4h required rescue medication on the first day of each Treatment Period while in Study MOR-9/92, 0% of patients receiving Kapanol® q24h and 17% of patients receiving MS Contin® on the first treatment day following the Lead-In Period needed rescue medication. In both of these studies, there was no statistical difference in the number of patients requiring rescue medication in the Kapanol® group and its respective comparator groups. These results, taken as a whole indicate that the need for rescue medication on the first day of treatment with Kapanol® is not different from the need for rescue when patients are transferred in a blinded manner from IRM solution to either IRM solution or MS Contin®.

When the Kapanol® treatment groups were stratified by the treatment received on the last day of the Lead-In Period (i.e., IRM solution or MS Contin®) there was no significant difference in the percentage of patients who used rescue medication on the first day of the Kapanol® Treatment Period, among the Lead-In Period and Kapanol® treatment group combinations. However, among the patients who used IRM solution during the Lead-In period, a greater proportion of patients in Kapanol® q24h treatment group used rescue medication on the first day of Kapanol® treatment and among the patients who used MS Contin® during the Lead-In Period, a greater proportion of patients in the Kapanol® q12h treatment group used rescue medication on the first day of Kapanol® treatment. Although these differences were not significant individually, overall they were significantly different from each other (p = 0.08). These relationships may be observed in Table 31. The clinical significance of these observations is unclear but may have arisen by chance given the small sample sizes in each of these groups.

TABLE 31
Proportion of Patients Who Used Rescue Medication on the First Day of the Kapanol® Treatment Period, Adjusting for the Lead-In Period Treatment Group (Study MOR-5/92)

Kapanol® Treatment Group	Use of Rescue Medication No	Yes	Total	Statistical Test/Results
Lead-In Treatment = IRM				
q12h	8 (73%)	3 (27%)	11	Fisher's exact test (2-tail)
q24h	4 (40%)	6 (60%)	10	p = 0.20
Total	12	9	21	
Lead-In Treatment = MS Contin®				
q12h	3 (33%)	6 (67%)	9	Fisher's exact test (2-tail)
q24h	6 (5%)	5 (45%)	11	p = 0.41
Total	9	11	20	

Cochran-Mantel-Haenzel Statistic p = 0.68
Breslow-Day Test - Homogeneity of the Odds Ratio p = 0.08

The amount of rescue medication (number of tablets) taken and the number of times doses of rescue medication were taken during the last day of the Lead-In Period and the first day of treatment with Kapanol® is presented in Table 32. As will be noted, the results of these analyses were nearly identical since, for the most part, patients took just one tablet each time they took rescue medication.

TABLE 32
Average Rescue Medication Taken by Kapanol® Treatment Group*
(Study MOR-5/92)

	Last Day of Lead-In Treatment Period		First Day of Kapanol® Treatment Period		
	q12h	q24h	q12h	q24h	Lead-In vs Treatment
n =	20	21	20	21	
Amt. of Rescue Doses of Rescue	0.25 ± 0.55	0.38 ± 0.67	1.00 ± 1.49	1.00 ± 1.30	p = 0.001
	0.25 ± 0.55	0.38 ± 0.67	0.90 ± 1.25	1.00 ± 1.3o	p = 0.001

* Data are presented as the mean ± the standard deviation.

The data indicate that there was no difference in the use of rescue medications within each of the two treatment periods for either of the Kapanol® groups on the first day of Kapanol® treatment, however, there was a statistically significant greater need for rescue medication on the first day of Kapanol® treatment than on the last day of the Lead-In period. As discussed above, the number of patients requiring rescue medication on the transition day from IRM solution to Kapanol® was higher in the present study than similar proportions when patients were transferred in a blinded fashion from IRM solution to Kapanol® in Studies MOBES-8/90 and MOR-9/92. It is highly likely that in the present study the unblinded transfer from formulations that were effective in controlling the patient's pain during Lead-In to an investigational drug of unknown efficacy may have played a role in the higher need for rescue medication on the first day of transfer.

Within the two treatment groups on the first day of Kapanol® treatment, the time to the first dose of rescue medication was significantly longer for the q24h group than for the q12h group. These results are presented in the form of a frequency distribution in Table 33.

TABLE 33
Frequency Distribution of Number of Hours to First Dose of Rescue Medication on the First Day of the Kapanol® Treatment Period*
(Study MOR-5/92)

Hours to First Dose of Rescue Medication	Kapanol® Treatment Group q12h	q24h	Total	Comparison of Groups
0 to 4	3 (33%)	3 (27%)	6	Fisher's exact test (2-tail)
4 to 8	5 (56%)	0 (0%)	5	p = 0.014
8 to 12	1 (11%)	1 (9%)	2	
12 to 16	0 (0%)	1 (9%)	1	
16 to 20	0 (0%)	2 (18%)	2	
20 to 24	0 (0%)	4 (36%)	4	
Total	9	11	20	

* Analysis is based on the 19 patients who took rescue medication on the first day of the Kapanol® treatment period.

Each of the nine times to first dose in the Kapanol® q12h treatment group were less than 12 hours; seven of the eleven times to first dose in the Kapanol® q24h treatment group exceeded 12 hours; the frequency distributions were significantly different according to Fisher's exact test.

Although there was a significant increase in the use of rescue medication during the transfer period from other opioids to Kapanol®, the proportion of patients who used rescue medication diminished as the Kapanol® Treatment Period progressed, to the point where there was no longer a significant difference between the proportion of patients who used rescue medication on the last day of the Lead-In Period and the proportion of patients who used rescue medication on the sixth day of Kapanol® treatment.

Comparison of VAS and VRS scores at various times after receipt of the first dose of Kapanol® during the transfer period are presented in Table 34 for the two Kapanol® groups and the groups combined. Changes reported are the scores on the last day of the Lead-In Period minus those on the first day of Kapanol® treatment. Thus, positive differences in ratings represent improvements while negative differences represent worsening of ratings relative to Lead-In. Kapanol® doses were taken at 10:00 AM (1000h).

TABLE 34
VAS and VRS Scores on the First Day of Kapanol® Treatment and Changes from Those Observed on the Last Day of the Lead-In Period[a]
(Study MOR-5/92)

Kapanol® q12h Treatment Group		Kapanol® q24h Treatment Group		Kapanol® Treatment Groups Combined	
Treatment	Change[b]	Treatment	Change[b]	Treatment	Change[b]
VAS Pain Intensity Scores at Time of Dosing (1000H)					
19.7 ± 22.3	-4.4 ± 13.4	13.2 ± 17.7	3.0 ± 11.9	16.3 ± 20.0	**-0.5 ± 13.0**
VAS Pain Intensity Scores at 1400H					
22.8 ± 25.6	-4.6 ± 20.0	16.7 ± 22.2	-8.1 ± 16.0	19.7 ± 23.8	**-6.3 ± 18.0**
VAS Pain Intensity Scores at 1800H					
17.9 ± 27.1	0.6 ± 15.7	15.5 ± 21.6	3.1 ± 22.8	16.6 ± 23.9	**2.0 ± 19.7**
VAS Pain Intensity Scores at 2200H					
24.3 ± 25.3	-5.4 ± 18.4	19.1 ± 23.6	-3.1 ± 18.8	21.6 ± 24.2	**-4.3 ± 18.4**
VAS Pain Intensity Scores at Trough Morphine Levels					
18.9 ± 20.8*	-3.6 ± 6.2*	16.3 ± 22.9	-0.6 ± 15.6	17.5 ± 21.7	**-2.0 ± 12.0**
VAS Pain Intensity Scores at Peak Morphine Levels					
21.2 ± 20.9	-7.1 ± 14.8	13.2 ± 19.4	0.3 ± 17.1	16.9 ± 20.2	**-3.0 ± 16.4**
VRS Pain Intensity Scores at Time of Dosing (1000H)					
0.85 ± 0.75	-0.11 ± 0.57	0.86 ± 0.73	0.05 ± 0.61	0.85 ± 0.73	**-0.03 ± 0.58**
VRS Pain Intensity Scores at 1400H					
1.11 ± 0.81	-0.28 ± 0.90	0.75 ± 0.90	-0.24 ± 0.90	0.92 ± 0.87	**-0.26 ± 0.89**
VRS Pain Intensity Scores at 1800H					
1.00 ± 0.91	-0.24 ± 0.56	0.76 ± 0.83	0.20 ± 0.83	0.87 ± 0.86	**0.00 ± 0.75**
VRS Pain Intensity Scores at 2200H					
1.20 ± 0.95	-0.32 ± 0.82	0.95 ± 0.97	-0.05 ± 0.85	1.07 ± 0.96	**-0.18 ± 0.83**
VRS Pain Intensity Scores at Trough Morphine Levels					
0.90 ± 0.79	-0.16 ± 0.69	1.00 ± 1.05	-0.15 ± 0.59	0.95 ± 0.92	**-0.15 ± 0.63**
VRS Pain Intensity Scores at Peak Morphine Levels					
1.11 ± 0.76**	-0.47 ± 0.62**	0.76 ± 0.83	0.00 ± 0.84	0.92 ± 0.81	**-0.21 ± 0.78**

a Data are presented as the mean ± the standard deviation.
b Change was defined as the value for the last day of the Lead-In Period minus that for the corresponding time on the first day of Kapanol® treatment.
* $p < 0.05$, lead-in vs treatment
** $p < 0.01$, lead-in vs treatment

000282

In the results reported above, there were no statistically significant differences between the two Kapanol® treatment groups. Statistically significant treatment effects were observed at the trough of plasma morphine concentrations for the Kapanol® q12h group for VAS scores; scores in the Kapanol® q12h group were higher indicating greater pain. The VRS scores at peak plasma morphine concentrations were also significantly different for the Kapanol® q12h treatment group with the pain score again higher in the Kapanol® q12h group. These results are consistent with a significantly lower peak plasma concentration normalized for dose for the Kapanol® q12h treatment group on the first day of treatment compared to the last day of the Lead-In Period (first day of Kapanol® Treatment Period, 0.162 ng/mL; last day of Lead-In Period, 0.301 ng/mL; p = 0.011). Also there was a significantly higher trough plasma morphine concentration normalized for dose for the Kapanol® q12h treatment group on the first day of treatment compared to the last day of the Lead-Period (first day of Kapanol® treatment Period, 0.187 ng/mL; last day of Lead-In Period, 0.136 ng/mL; p = 0.005). An unexpected result during Kapanol® Treatment was a lower morphine blood level during peak than during trough for the Kapanol® q12h treatment group. This is a reflection of the relatively flat plasma morphine level over time on multiple dosing with Kapanol® on a q12h regimen and of the variations in actual times that the blood samples were taken. None of the other comparisons of dose normalized trough and peak plasma morphine concentrations were statistically significant between the last day of the Lead-In Period and the first day of Kapanol® treatment. These data are consistent with the remaining data for the VAS and VRS scores reported above.

In general, the mean quality of sleep and the mean assessment of morning pain intensity was better during Treatment compared to the last day of Lead-In. These differences were not significant and did not differ between the two Kapanol® treatment groups. The average rating of morning pain intensity was between no pain and mild pain in each of the Kapanol® groups on most days of treatment.

In general, although the evening assessment of pain control during Days 2 through 7 of the Kapanol® treatment period indicated slightly increased pain during treatment compared to during the last day of the Lead-In Period, these differences were not statistically significant. As with the morning pain intensity assessment, there were no significant differences in the evening pain assessments between the two Kapanol® treatment groups.

One of the factors of importance in evaluating the efficacy of Kapanol® treatment compared to treatment in the Lead-In Period with IRM solution and MS Contin® was the patient treatment preference and investigator global assessment of efficacy at the end of the 7-day Kapanol® Treatment Period, with the patient evaluation having greater importance. The results of these two assessments are presented in Table 35.

TABLE 35
Patient Treatment Preference and Investigator Global Assessments
(Study MOR-5/92)

Patient/Investigator	Assessment	Kapanol® Group q12h	Kapanol® Group q24h
Patient Treatment Preference	Kapanol® Treatment	15 (83%)	16 (84%)
	No Treatment Preference	1 (6%)	2 (11%)
	Previous Analgesic Treatment	2 (11%)	1 (5%)
Investigator Global Assessment	Marked Efficacy	12 (67%)	10 (53%)
	Moderate Efficacy	4 (22%)	8 (42%)
	Minimal Efficacy	2 (11%)	1 (5%)

Greater than eighty percent of the patients preferred Kapanol® to their previous treatment while investigators rated Kapanol® as having marked efficacy for more than half of the patients in spite of the reported differences in pain control on the first day of Kapanol® treatment.

It is very likely that the results of pain control and intensity on the first day of Kapanol® treatment were related to patient anxiety related to the fact that they knew they were being switched from treatment regimens that "worked" to an investigational drug of unknown analgesic potency. The fact that pain control on subsequent days of Kapanol® treatment, as the patients became comfortable with the medication, was assessed to be no different than that which they had experienced during the Lead-In Period, supports the hypothesis that the patients may have been anxious on the day of transition. Within several days of treatment, both Kapanol® treatments proved to be as efficacious as IRM solution and MS Contin®, and indeed, were preferred by the majority of patients.

5. Analysis of Dose-Response or Blood Level-Reponse Data

Kadian™ is an opioid analgesic for the management of moderate to severe chronic cancer pain. As such, morphine formulations, including Kadian™, have found their greatest utility as third step agents on the WHO Three-Step Analgesic Ladder when patients have reached the point where pain control cannot be provided with a combination of non-opioid medications (NSAIDs and acetaminophen) and intermittent use of moderate or strong opioids. Kadian™ is most useful when the patient requires a constant level of opioid analgesia as a "floor" or "platform" from which to manage breakthrough pain.

The following information regarding the relationships between morphine dose, blood levels, and analgesia are described in the class labeling for morphine and the proposed labeling for Kadian™.

In any particular patient, analgesia and plasma morphine concentrations are related to the morphine dose. In non-tolerant individuals, plasma morphine concentration-efficacy relationships have been demonstrated and suggest that opiate receptors occupy effector compartments, leading to a lag-time, or hysteresis, between rapid changes in plasma morphine concentrations and effects of such changes. The most direct and predictable concentration-effect relationships can, therefore, be expected at distribution equilibrium and/or steady state conditions. In general, the minimum effective analgesic concentration in the plasma of non-tolerant patients ranges from approximately 10 - 50 ng/mL, corresponding to the range of blood levels expected after a single intra-muscular dose of 5 - 10 mg. The toxic dose in this setting varies widely, ranging from a low of 10 - 15 mg in the elderly, vulnerable patient, to doses of 30 - 50 mg tolerated by healthy volunteers and to several grams for opioid-tolerant patients.

While plasma morphine-efficacy relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. Some patients may become rapidly tolerant to the analgesic effects of morphine, and will require doses 10 - 50 times (or greater) than the appropriate dose for opioid-naive individuals. It is for this reason, that in opioid-tolerant individuals there is no correlation between plasma morphine concentration and analgesia. Since the development of tolerance to both the therapeutic and adverse effects of opioids is highly individualized, the dose of morphine should be individually titrated to the patient's condition and should not be based on an arbitrary choice of a dose or blood level to be obtained.

The patients who have been studied for this NDA have all been patients with moderate to severe chronic cancer pain in which pain has been managed with either IRM in the form of solution or tablets or MS Contin®. Because of the complex relationships between morphine dose, plasma concentrations, and analgesic efficacy, it has not been possible to systematically assess these relationships in this patient population. It has been well documented in this NDA, however, that patients who have been titrated to stable doses of IRM or MS Contin® may be successfully transferred to equivalent daily doses of Kadian™, either q12h or q24h, without loss of efficacy.

The dose equivalence of Kadian™, IRM, and MS Contin® although they all have widely differing rates of dissolution and absorption, all show an oral bioavailability of 20 - 40%, a volume of distribution (V_d) of 2 - 4 liters/kg, a clearance of 0.9 - 1.2 liters/kg/hr, and a terminal half-life of 2 to 4 hours. For IRM, following oral administration, approximately fifty percent of the morphine that will ever reach the central compartment intact, reaches it within 30 minutes. Following the administration of Kadian™ to healthy volunteers, however, this extent of absorption occurs, on average, after 8 hours. Despite the lower rate of absorption of Kadian™, the extent of metabolism to morphine-3-glucuronide and morphine-6-glucuronide is not different from that of IRM.

Steady-state, dose-normalized plasma morphine concentrations from patients receiving IRM solution q4h and Kapanol® q12h are presented in Figure 7. Data comparing Kapanol® q12h with MS Contin® q12h are presented in Figure 8. As noted below, these data were derived from Study MOB-1/90.

FIGURE 7. Comparison of Steady-State, Dose-Normalized Plasma Morphine Concentrations in Patients Receiving IRM solution q4h and Kapanol® q12h (Study MOB-1/90)

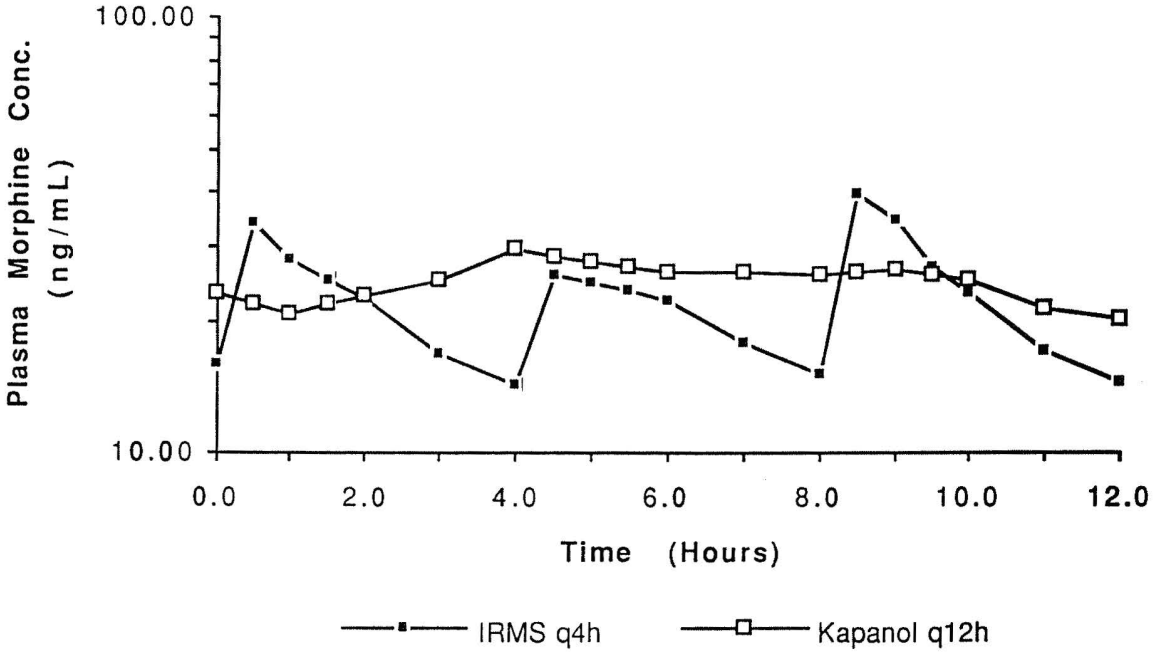

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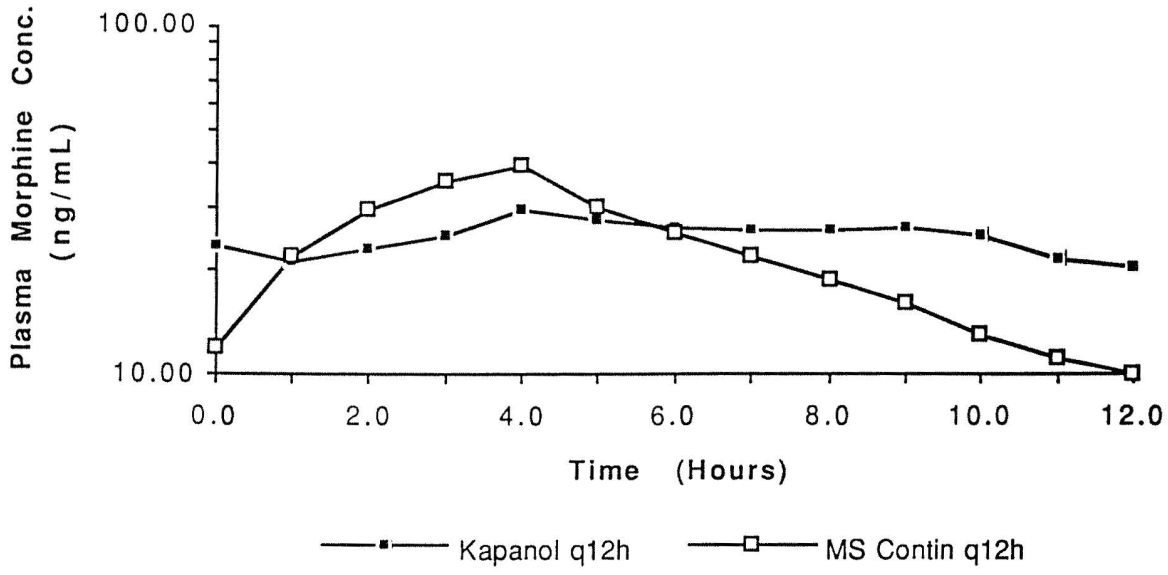
FIGURE 8. Comparison of Steady-State, Dose-Normalized Plasma Morphine Concentrations in Patients Receiving Kapanol® q12h and MS Contin® q12h (Study MOB-1/90)



At any fixed dose and dosing interval at steady state, Kadian™ has a significantly lower C_{max} and higher C_{min} than IRM solution, but is therapeutically similar with regard to pain control and adverse events. This relationship is also true for the comparison between Kadian™ and MS Contin®, i.e., Kadian™ has a significantly lower C_{max} and higher C_{min} than MS Contin®.

All of the clinical studies reported in this application contain a built-in bias against Kadian™ by virtue of the patient selection process. Patients were only eligible for inclusion if they could be titrated to a stable daily dose of either IRM solution or MS Contin® both of which exhibit wide fluctuations in their plasma concentration-time curves. Through the selection process, patients sensitive to the dose-response effects of morphine or to wide changes in plasma concentration were effectively screened out. It is this type of patient who would potentially gain the most benefit from the smoother plasma concentration/time profile provided by Kadian™.

6. Analysis of responses in Subsets of the Overall Population

Morphine is a drug that has been well characterized as a result of extensive use over many decades in the management of chronic pain. It is well known that morphine should be administered with caution, and in reduced dosages in elderly or debilitated patients, patients with severe renal or hepatic insufficiency, patients with Addison's disease, myxodema, hypothyroidism, and prostatic hypertrophy or urethral stricture.

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Caution should also be exercised in the administration of morphine to patients with CNS depression, toxic psychosis, acute alcoholism or delirium tremens, severe kyphoscoliosis, convulsive disorders, patients about to undergo biliary surgery, and patients with acute pancreatitis secondary to biliary tract disease.

One of the studies conducted for this NDA, CDD-14556, was of sufficient size to allow assessment of the responses in subsets of the overall population. This study completed 152 patients treated for moderate to severe cancer pain in 28 centers in the US. Because the protocol explicitly excluded patients with many of the medical conditions listed above, the subsets examined were as follows:

- titrated dose equal to or above 110mg/day or below 110 mg/day;
- gender;
- race; and
- age less than 65 years or 65 years and older.

These subsets are considered below.

a. Titrated IRM Dose Below 110 mg/Day and Equal to or Above 110 mg/Day

The patients who completed the Final Day of the study were partitioned into two subgroups based on the stable, titrated dose of IRM obtained during the Lead-In Period. These doses were below 110 mg/day (low dose) and equal to or above 110 mg/day (high dose). Efficacy data for patients titrated to these dose levels are presented in Table 36.

TABLE 36
Efficacy on Final Day by Titrated Dose Level for All Completed Patients (Study CDD-14556)

Variable	Kapanol® q24h	Kapanol® q12h	MS Contin® q12h	p-values (a) L	T	LxT
Number of Patients						
Dose < 110 mg/day	29 (54%)	23 (51%)	29 (55%)			
Dose ≥ 110 mg/day	25 (46%)	22 (49%)	24 (45%)			
Elapsed Time (h) to:				0.168	0.001	**0.041**
Remedication						
Dose < 110 mg/day						
Mean	18.1	9.6	8.3			
95% CI (b)	15.8, 20.5	6.9, 12.2	6.0, 10.7			
Dose ≥ 110 mg/day						
Mean	13.6	8.6	9.1			
95% CI	11.1, 16.2	5.9, 11.3	6.5, 11.7			
Difference	-4.5	-1.0	0.8			
First Rescue				0.075	0.935	0.270
Dose < 110 mg/day						
Mean	18.1	17.4	14.0			
95% CI	14.7, 21.5	13.6, 21.2	10.6, 17.4			
Dose ≥ 110 mg/day						
Mean	13.6	13.6	14.7			
95% CI	10.0, 17.3	9.7, 17.5	11.0, 18.4			
Difference	-4.5	-3.8	0.7			
Total Rescue in 24 Hours				0.005	0.916	**0.551**
mg						
Dose < 110 mg/day						
Mean	10.1	8.5	20.1			
95% CI	-7.1, 27.2	-11, 27.7	2.7, 37.6			
Dose ≥ 110 mg/day						
Mean	44.0	36.1	36.6			
95% CI	24.8, 63.3	16.4, 55.8	17.7, 55.4			
Difference	33.9	27.7	16.4			
% IRM (c)				0.638	0.655	0.552
Dose < 110 mg/day						
Mean	19.3	14.6	30.1			
95% CI	6.1, 32.5	-0.3, 29.4	16.6, 43.5			
Dose ≥ 110 mg/day						
Mean	14.8	15.3	14.9			
95% CI	0.0, 29.7	0.1, 30.4	0.4, 29.5			
Difference	-4.5	0.7	-15.1			

(a) P-values are from the F test of ANOVA for titrated dose level (L), treatment effect (T) and titrated dose level by treatment interaction (LxT).
(b) The 95% CI (confidence interval) was computed using the mean squared error from the analysis of variance.
(c) % IRM is the percent of the titrated daily immediate-release morphine sulfate dose level.

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In the results reported above, the only significant treatment by dose level interaction observed was related to the elapsed time to remedication; this indicates that the difference between means was not consistent across the partition. There was a highly significant treatment effect for the time to remedication in which the time for the Kapanol® q24h was significantly longer than for either of the other two treatments, similar to that which was reported for the population as a whole in Table 3. As discussed with the data in Table 3, the significantly longer time to remedication in the Kapanol® q24h group is an artifact of the study design in which the time to remedication may have been to either rescue medication or the next scheduled dose of study agent. Because the second daily dose of Kapanol® q12h and MS Contin® q12h was administered before the next dose of Kapanol® q24h, the time to remedication was shorter in the former two groups.

The statistically significant treatment effect was not observed, however, when only the patients who required rescue medication were considered. In addition, there was a significantly greater need for rescue medication in patients requiring 110 mg/day or more. This difference was not observed when the amount of rescue medication was expressed as a percent of the titrated IRM dose indicating that the increased use of rescue medication by this patient population was merely a reflection of their greater overall need for morphine for effective pain control. There is no indication from these data that the group having the highest requirement for morphine, who are both morphine-tolerant and at least moderately sensitive to both under-analgesia and withdrawal, were under-dosed.

b. Gender

Table 37 presents effect of gender on the major efficacy parameters.

TABLE 37
Efficacy on Final Day by Gender for All Completed Patients (Study CDD-14556)

Variable		Kapanol® q24h	Kapanol® q12h	MS Contin® q12h	p-values (a) G	T	GxT
Number of Patients							
Female		29 (54%)	16 (36%)	28 (53%)			
Male		25 (46%)	29 (64%)	25 (47%)			
Elapsed Time (h) to:					0.941	0.001	**0.388**
Remedication							
Female							
Mean		16.9	9.1	8.2			
95% CI (b)		14.5, 19.3	5.9, 12.4	5.7, 10.6			
Male							
Mean		15.1	9.1	9.2			
95% CI		12.5, 17.7	6.6, 11.5	6.6, 11.8			
	Difference	1.8	0.1	-1.0			
First Rescue					0.853	**0.963**	**0.531**
Female							
Mean		16.9	15.9	12.7			
95% CI		13.4, 20.3	11.2, 20.5	9.2, 16.2			
Male							
Mean		15.1	15.4	16.2			
95% CI		11.3, 18.8	11.9, 18.8	12.5, 19.9			
	Difference	1.8	0.5	-3.5			
Total Rescue in 24 Hours					0.902	0.900	**0.493**
mg							
Female							
Mean		19.3	11.3	36.4			
95% CI		1.3, 37.3	-13, 35.1	18.4, 54.4			
Male							
Mean		31.9	27.9	17.6			
95% CI		12.4, 51.3	10.2, 45.6	-1.9, 37.1			
	Difference	-12.6	-16.7	18.8			
% IRM (c)					0.225	0.631	**0.967**
Female							
Mean		19.8	15.1	28.0			
95% CI		6.4, 33.2	-2.7, 32.9	14.6, 41.5			
Male							
Mean		14.5	14.8	17.3			
95% CI		-0.0, 29.0	1.6, 28.0	2.8, 31.8			
	Difference	5.3	0.3	10.7			

(a) P-values are from the F test of ANOVA for gender effect (G), treatment effect (T) and gender level by treatment interaction (GxT).
(b) The 95% CI (confidence interval) was computed using the mean squared error from the analysis of variance.
(c) % IRM is the percent of the titrated daily immediate-release morphine sulfate dose level.

As observed in the previous table, there was a statistically significant treatment effect for the elapsed time to remedication among the patients who completed the study. This effect was in favor of a longer time to remedication for patients treated with Kapanol® q24h and is regarded as an artifact of the study design as discussed for Table 34. This effect is similar to that observed in the population as a whole. The effect was not observed when only the patients who required rescue medication were considered either for the effect of gender or for the population as a whole. No other statistically significant differences were identified, particularly those related to effects of gender.

c. Race

The subgroup analysis for race is summarized in Table 38. There were a total of 25 Blacks and 118 Caucasians who completed the study. The remaining 9 patients consisted of 8 Hispanics and one Pakistani. Only the Blacks and Caucasians were included in the analysis of racial subgroups.

TABLE 38
Efficacy on Final Day by Race for All Completed Patients (Study CDD-14556)

Variable		Kapanol® q24h	Kapanol® q12h	MS Contin® q12h	p-values (a) R	T	RxT
Number of Patients							
Black		8 (16%)	9 (21%)	8 (16%)			
Caucasian		43 (84%)	34 (79%)	41 (84%)			
Elapsed Time (h) to:					0.198	0.024	0.144
Remedication							
Black							
Mean		14.1	11.0	8.4			
95% CI (b)		9.6, 18.6	6.7, 15.2	3.8, 12.9			
Caucasian							
Mean		16.4	9.0	8.8			
95% CI		14.4, 18.3	6.8, 11.2	6.8, 10.8			
	Difference	2.3	-2.0	0.4			
First Rescue					0.289	0.115	0.074
Black							
Mean		14.1	21.7	12.9			
95% CI		7.7, 20.5	15.7, 27.7	6.5, 19.2			
Caucasian							
Mean		16.4	14.7	14.6			
95% CI		13.6, 19.1	11.6, 17.8	11.8, 17.4			
	Difference	2.3	-7.0	1.8			
Total Rescue in 24 Hours					0.187	0.206	0.042
mg							
Black							
Mean		13.9	10.0	52.5			
95% CI		-22.0, 49.9	-22.0, 41.7	18.9, 86.1			
Caucasian							
Mean		26.6	25.6	24.8			
95% CI		11.9, 41.3	9.3, 41.9	9.7, 39.8			
	Difference	12.7	15.6	-27.7			
% IRM (c)					0.675	0.521	0.855
Black							
Mean		22.2	4.2	19.4			
95% CI		-4.2, 48.6	-19.0, 27.5	-5.3, 44.2			
Caucasian							
Mean		14.2	17.5	25.1			
95% CI		3.4, 25.0	5.5, 29.5	14.1, 36.2			
	Difference	-8.0	13.4	5.7			

(a) P-values are from the F test of ANOVA for race level (R), treatment effect (T) and race level by treatment interaction (RxT).
(b) The 95% CI (confidence interval) was computed using the mean squared error from the analysis of variance.
(c) % IRM is the percent of the titrated daily immediate-release morphine sulfate dose level.

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There was a statistically significant interaction between race and treatment with respect to total rescue in 24 hours. The difference between the mean responses of the Blacks and Caucasians in the MS Contin® q12h treatment group was in the opposite direction from the difference in either the Kapanol® q12h or the Kapanol® q24h treatment. When only those patients who needed rescue medication were considered the interactions were not statistically significant. There was a statistically significant treatment effect with respect to elapsed time to remedication in which the Kapanol® q24h treatment group had a longer time to remedication than either of the other two treatment groups. As discussed previously this observation is an artifact of the study design due to differences in the time to remedication with study agents in the various treatment groups. The race effect on the time to remedication was not statistically significant when only patients who required rescue medication were considered.

d. Age: Under 65 Years or 65 Years and Older

Table 39 summarizes the analyses for differences due to the effect of age. The patients were partitioned into an "under 65 years" group and an "equal to or greater than 65 years" group.

TABLE 39
Efficacy on Final Day by Age for All Completed Patients (Study CDD-14556)

Variable		Kapanol® q24h	Kapanol® q12h	MS Contin® q12h	p-values (a) A	T	AxT
Number of Patients							
< 65 Years		34 (63%)	25 (56%)	28 (53%)			
≥ 65 Years		20 (37%)	20 (44%)	25 (47%)			
Elapsed Time (h) to:					0.215	0.001	0.747
Remedication							
< 65 Years							
Mean		15.4	9.1	7.6			
95% CI (b)		13.1, 17.6	6.5, 11.7	5.1, 10.0			
≥ 65 Years							
Mean		17.2	9.1	9.9			
95% CI		14.3, 20.1	6.1, 12.0	7.3, 12.5			
	Difference	1.8	-0.1	2.3			
First Rescue					0.258	0.929	0.524
< 65 Years							
Mean		15.4	15.9	11.8			
95% CI		12.2, 18.5	12.2, 19.6	8.4, 15.3			
≥ 65 Years							
Mean		17.2	15.1	17.1			
95% CI		13.1, 21.3	11.0, 19.3	13.4, 20.8			
	Difference	1.8	-0.8	5.3			
Total Rescue in 24 Hours					0.549	0.999	0.370
mg							
< 65 Years							
Mean		35.2	16.5	28.9			
95% CI		18.4, 51.9	-2.5, 35.5	11.0, 46.9			
≥ 65 Years							
Mean		9.0	28.9	26.3			
95% CI		-12, 30.2	7.6, 50.1	6.9, 45.7			
	Difference	-26.2	12.4	-2.6			
% IRM (c)					0.563	0.553	0.583
< 65 Years							
Mean		18.7	14.8	19.4			
95% CI		6.1, 31.3	0.6, 29.1	6.0, 32.9			
≥ 65 Years							
Mean		15.2	15.0	27.4			
95% CI		-0.7, 31.1	-0.9, 30.9	12.8, 41.9			
	Difference	-3.5	0.2	7.9			

(a) P-values are from the F test of ANOVA for age level (A), treatment effect (T) and age level by treatment interaction (AxT).
(b) The 95% CI (confidence interval) was computed using the mean squared error from the analysis of variance.
(c) % IRM is the percent of the titrated daily immediate-release morphine sulfate dose level.

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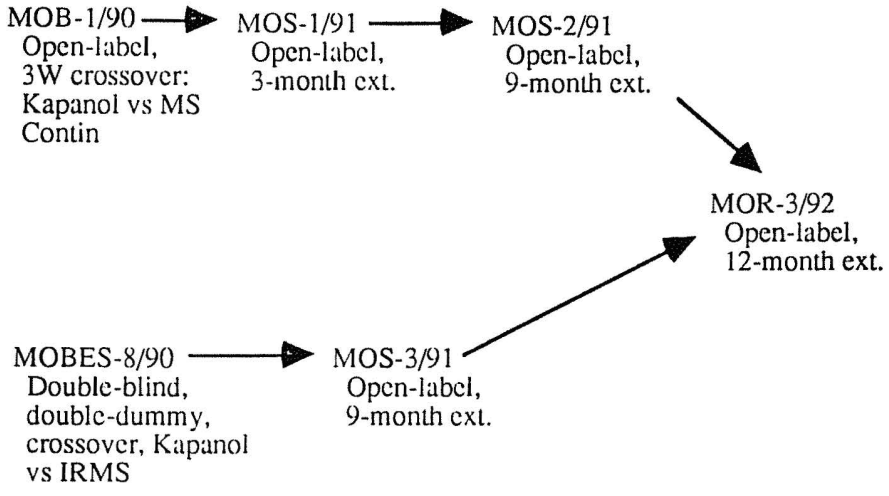
There were no statistically significant interactions between age and treatment. However, one statistically significant effect of treatment was observed with respect to the elapsed time to remedication with the Kapanol® q24h treatment group exhibiting the longest time to remedication. This reflects the population as a whole in which the Kapanol® q24h treatment group required a significantly longer time to remedication; this observation, as discussed above, is an artifact of the study design. As with prior analyses, when only patients who required remedication were considered, no significant effect of treatment was found on the time to remedication.

7. Evidence of Long-Term Efficacy, Tolerance and Withdrawal Effects

Long-term effectiveness of Kadian™ has been demonstrated in three open-label extension studies that evaluated patients for a total of up to 24 months. Study MOS-1/91 was an open-label 12 week extension of study MOB-1/90. Two nine-month studies, MOS-2/91 and MOS-3/91, were conducted that were extensions of Studies MOB-1/90 and MOS-1/91 for Study MOS-2/91 and Study MOBES-8/90 for Study MOS-3/91. Patients who completed studies MOS-2/91 and MOS-3/91 were eligible to enter the 12-month open-label extension, Study MOR-3/92. The relationships between these studies, previously presented as Figure 6, is shown diagrammatically below.



Patients enrolled in the study sequence beginning with Study MOB-1/90 and who completed the sequence received over 24 months of therapy with Kapanol® q12h and those enrolled in and who completed the study sequence beginning with Study MOBES-8/90 received over 21 months of treatment with Kapanol® q12h.

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In all of these studies Kadian™ was well-tolerated and pain control continued to be acceptable through the end of the 12-month extension study. There was no indication that patients with the highest dose requirements who are tolerant to the effects of morphine and very sensitive to morphine withdrawal were under-dosed with long-term treatment of Kadian™.

During the open-label extension studies, dose escalations were permitted and were necessary in some patients. Dose escalations were not related to the development of tolerance to the analgesic effects of Kapanol® but rather to progression of the patient's underlying disease.

Published reports on the clinical testing of morphine formulations for drug abuse potential have included healthy subjects, opioid abusers or ex-addicts, and patients receiving morphine for therapeutic purposes.

While the development of tolerance and physical dependence was confirmed in all of these populations, several studies in patients with cancer pain have shown that drug abuse and psychological dependence did not occur in this group of patients. As in the patient population examined in this NDA, the major reason for escalation of drug intake was progression of metastatic disease with increasing severity of pain (Kanner and Foley, 1981; Chapman and Hill, 1989; and Collin et al, 1993).

Patients treated for chronic cancer pain may become physically dependent on morphine without becoming addicted to it (Kanner and Foley, 1981; Chapman and Hill, 1989; Collin et al, 1993; and Portenoy, 1993). Tolerance to the analgesic effects of morphine is not a significant problem in the treatment of cancer pain (Warfield, 1993) since several studies have shown that patients with stable disease (malignant or non-malignant in origin) can be maintained on the same dose of analgesic for extremely long periods.

Specific studies have not been conducted on withdrawal effects following abrupt removal of Kadian™ therapy or after administration of an opiate antagonist. Physical dependence occurs within 3 to 4 weeks in most patients receiving daily opioid analgesics although it may occur more rapidly. Many physicians and medical practitioners have confused the terms drug dependency and addiction when patients are treated with opioids chronically for the relief of pain or other medical disorders. It is true that most patients who require opioids for medical purposes may develop tolerance and physical dependence but, as the medical requirement for these drugs declines, there is remarkably little sustained abuse (Cicero, 1992).

Kadian™, when used as directed, represents no greater risk of abuse or addiction when used for chronic moderate to severe pain, than other current forms of morphine therapy. The pharmacokinetic profile of Kadian™ suggests that, in its marketed formulation, it may have a lower abuse liability, particularly in the opioid naive patient, due to its slow onset of action, prolonged duration of action and minimal fluctuations in peak to trough morphine plasma concentrations.

8. Summary and Conclusions

The clinical program for Kadian™, which was developed in close consultation with the staff of the Pilot Drug Evaluation Staff of the FDA through the interactive IND process, enables a number of conclusions to be drawn regarding the efficacy of Kadian™ compared to commercially available morphine formulations. These conclusions are summarized below:

a. In the management of moderate to severe chronic pain, Kadian™ administered both every 24 hours and every 12 hours has an efficacy profile clinically and statistically similar to that of MS Contin® q12h and IRM q4h when assessed using established measures of efficacy.

b. In those studies in which Patient Global Assessments of Pain Control were recorded, including both the controlled and uncontrolled clinical trials, pain control with Kadian™ q24h and q12h was graded as acceptable. In controlled studies which included comparator drugs, either IRM or MS Contin®, pain control was similar to that with Kadian™.

c. In those studies in which Investigator Global Assessments of Efficacy were recorded, including both the controlled and uncontrolled clinical trials, investigators judged that Kadian™ q24h and q12h provided marked to moderate efficacy. Similar evaluations were obtained for IRM and MS Contin® in the controlled clinical trials that contained these comparator drugs.

d. When converting patients from immediate-release morphine, the first dose of Kadian™ should be given with the last dose of the immediate-release formulation.

e. In two double-blind, double-dummy controlled clinical trials, Studies MOBES-8/90 and MOR-9/92, there were no differences in the use of rescue medication on the first day of treatment with Kadian™ q12h and q24h compared to the last day of treatment with immediate-release morphine q4h or controlled-release MS Contin® q12h. Therefore, patients stabilized to adequate clinical effect with other oral morphine formulations may be safely transferred to Kadian™ at the same total daily morphine dose.

f. During the long-term open-label studies of Kadian™ q12h, there was no indication of dimunition of analgesia in patients with cancer treated for up to 24 months. Dose escalations that did occur were consistent with disease progression.

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7. CLINICAL DATA SUMMARY

D. Safety Summary

NDA Volume 101

1. Overall Extent of Exposure

a. Healthy Subjects

A total of 177 healthy subjects received one or more doses of Kadian™, controlled-release morphine tablets, or immediate-release morphine solution in single-dose crossover studies (Table 1). One hundred fifty-eight of these subjects received Kadian™ doses ranging from 30 to 100 mg (mean, 52.9 mg); the most frequently received dose was 50 mg.

Table 1
Extent of Exposure: Healthy Subjects:
Single-Dose, Crossover Studies[a]

	Kadian™	Morphine CR[b]	IR Morphine Solution[c]	One or More Trts
No. of subjects	158	43	54	177
Total no. of exposures[d]	425	54	54	533
No. of exposures/subject				
1	29	32	54	13
2	31	11	–	12
3	58	–	–	112
4	40	–	–	40
Mean (± SD) dose (mg)	52.9 ± 13.5	60.0 ± 0.0	25.0 ± 0.0	NA
Distribution of doses received:				
25 mg	-	-	54	NA
30 mg	25	-	-	NA
50 mg	350	-	-	NA
60 mg	--	54	-	NA
70 mg	26	-	-	NA
100 mg	24	-	-	NA

a Studies MOBU-7/90-2, 083-031, KAP-RRC/91/01, MOR-13/94, MOBU-9/90, MOR-8/92, and MOBU 10/90
b MS Contin® or MST Continus®
c Immediate-release morphine solution
d In some studies subjects received more than one dose or formulation of the product.

C00299

b) Patients with Cancer

A total of 337 patients with chronic cancer pain participated in controlled (n=296) and/or uncontrolled (n=88) studies. The extent of exposure to Kadian™ and comparative drugs in these studies is summarized in the following sections.

i. Controlled Studies

A total of 296 patients received treatment with Kadian™ (n=227) and/or comparative drugs in controlled clinical trials. The number of patients exposed to each treatment, including patients who received more than one treatment in crossover evaluations, is summarized for each controlled study in Table 2. The duration of treatment for each period in each study was 7 days.

Table 2
Number of Patients Exposed to Each Treatment:
Controlled Studies in Patients with Cancer[a]

	Kadian™	Morphine CR[b]	IR Morphine Solution[c]
No. of Patients Exposed			
Study 14556			
q12h	61	62	-
q24h	65	-	-
Study MOB-1/90	29	27	29
Study MOR-9/92	29	26	-
Study MOBES-8/90	26	-	26
Study MOR-2/92	17[d]	11	-
All Studies	227	126	55

a All studies were crossover trials except for study 14556, which was a parallel-group study. For crossover studies, exposures in each treatment period are represented (i.e., patients may be counted in more than one column).

b MS Contin® or MST Continus®

c Immediate-release morphine solution

d Includes six patients who received two periods of Kadian™ treatment (q12h and q24h regimens).

Kadian™ daily doses received by patients in controlled clinical trials are summarized in Table 3. Nearly 50% of patients received daily Kadian™ doses of less than 120 mg (or < 2 mg/kg), with a maximum daily dose of 1500 mg (33.3 mg/kg). The mean daily dose administered during the 7-day treatment periods of the controlled studies was 184 mg, and the median daily dose was 120 mg. The median daily dose was 120 mg for Kadian™ and the immediate-release morphine solution, and 115 mg for controlled-release morphine tablets; adjusted for body weight, the median daily dose was 1.7 mg/kg for all three formulations.

C00300

Table 3
Summary of Mean Daily Kadian™ Dose: Controlled Studies in Patients with Cancer

		Crossover Studies[a] N=101	Study 14556 (parallel-group) q12h N=61	q24h N=65	All Studies N=227
Daily Kadian™ Dose (mg) number (%) of patients					
< 120		44 (44%)	29 (48%)	33 (51%)	106 (47%)
120 - 240		35 (35%)	24 (39%)	22 (34%)	81 (36%)
> 240		22 (22%)	8 (13%)	10 (15%)	40 (18%)
Total	mean ± SD	235 ± 308	143 ± 109	145 ± 146	184 ± 231
	median	120	120	90	120
	range	40-1500	25-585	30-800	25-1500
Daily Kadian™ Dose (mg/kg)[b] number (%) of patients					
< 2 mg/kg		52 (52%)	35 (57%)	41 (63%)	128 (56%)
2 - 4 mg/kg		23 (23%)	17 (28%)	12 (18%)	52 (23%)
> 4 mg/kg		21 (21%)	7 (11%)	10 (15%)	38 (17%)
Total	mean ± SD	3.7 ± 5.3	2.1 ± 1.7	2.1 ± 2.1	2.8 ± 3.9
	median	1.8	1.7	1.4	1.7
	range	0.4-33.3	0.4-8.0	0.3-10.5	0.3-33.3

[a] Studies MOB-1/90, MOR-9/92, MOBES-8/90, and MOR-2/92. Includes both Kadian™ treatment periods for six patients in study MOR-2/92 who received Kadian™ on a q12h and q24h regimen.

[b] Weight was not recorded for some patients; thus the 'n' for dose in mg/kg is less than the 'n' for dose in mg.

The number of patients who received Kadian™ or comparative drugs during the first treatment period of crossover studies (and during each period of the parallel study 14556) is summarized in Table 4. The total number of patients (n=296) reflects the number of individuals treated in these studies.

Table 4
Number of Patients Exposed in the First Treatment Period:
Controlled Studies in Patients with Cancer[a]

	Kadian™	Morphine CR[b]	IR Morphine Solution[c]
No. of Patients Exposed			
Study 14556			
q12h	61	62	-
q 24h	65	-	-
Study MOB-1/90	12	9	13
Study MOR-9/92	15	14	-
Study MOBES-8/90	14	-	13
Study MOR-2/92	12	6	-
All Studies	179	91	26

a All studies were crossover trials except for Study 14556, which was a parallel-group study. For crossover studies, only the first treatment period is represented (i.e., patients are counted in only one column).
b MS Contin® or MST Continus®
c Immediate-release morphine solution

ii. Uncontrolled Studies

A total of 88 patients received Kadian™ in long-term, open-label extension studies (n=47) or in an open-label parallel comparison of the q12h and q24h regimens (n=41). Most patients in the extension studies received daily Kadian™ doses of 240 mg or less (mean, 233 mg; median, 140 mg); the maximum daily dose was 1500 mg (Table 5). The majority of patients in study MOR-5/92 received daily Kadian™ doses of less than 120 mg.

The total duration of treatment in the long-term extension studies ranged from 9 to 685 days (mean, 188 days). Most patients in those studies received open-label Kadian™ treatment for 6 months or less, with a median duration of 103 days. Two patients received treatment for 6 to 9 months; six patients, for 9 to 12 months; and seven patients received more than 1 year and up to nearly 2 years of Kadian™ treatment (median, 563 days).

C00303

Table 5
Summary of Daily Kadian™ Dose and Duration of Treatment:
Uncontrolled Studies in Patients with Cancer[a]

		Long-Term Extension Studies[b] N=47	Study MOR-5/92 q12h N=20	Study MOR-5/92 q24h N=21
Daily Kadian™ Dose (mg)[c] number (%) of patients				
< 120		14 (30%)	12 (60%)	9 (43%)
120 - 240		20 (43%)	6 (30%)	8 (38%)
> 240		13 (28%)	2 (10%)	4 (19%)
Total	mean ± SD	233 ± 272	124 ± 86	166 ± 147
	median	140	90	120
	range	40-1500	40-360	20-600
Daily Kadian™ Dose (mg/kg)[c,d] number (%) of patients				
< 2 mg/kg		23 (49%)	13 (65%)	13 (62%)
2 - 4 mg/kg		13 (28%)	5 (25%)	3 (14%)
> 4 mg/kg		9 (19%)	1 (5%)	5 (24%)
Total	mean ± SD	3.4 ± 5.2	1.8 ± 1.2	2.7 ± 3.1
	median	2.0	1.5	1.6
	range	0.4-33.3	0.6-4.9	0.4-14.3
Duration of Treatment (days)				
N		47	20	21
Mean ± SD		188 ± 182	6.3 ± 1.9	6.2 ± 1.6
Median		103	7	6
Range		9-685	2-8	2-8
Number of pts treated for:				
≤ 90 days		22	20	21
91-181 days		10	----	---
182-274 days		2	----	----
274-365 days		6	----	----
366-730 days		7	----	----

a Includes open-label, long-term extension studies and open-label, parallel-group study MOR-5/92.

b Open-label follow-up period of study MOBES-8/90 and studies MOS-1/91, MOS-2/91, MOS-3/91, and MOS-3/92. All patients in these studies received Kadian™ on a q12h regimen. There were two sequential combinations of these studies; patients' total experience during the sequence of studies was linked for each exposure variable.

c Highest daily Kadian™ dose (mean ± SD) for the long-term extension studies.

d Weight was not recorded for some patients; thus the 'n' for dose in mg/kg is less than the 'n' for dose in mg.

2. Adverse Events in Clinical Trials

a. Adverse Events in Healthy Volunteers

Adverse events reported in the seven single-dose crossover studies in healthy volunteers are summarized below in Table 6, by treatment, for all adverse events and for adverse events that were considered possibly, probably, or definitely related to treatment.

C00304

i. All Adverse Events

As described previously, 177 healthy subjects received one or more doses of Kadian™, controlled-release morphine tablets, or immediate-release morphine solution in single-dose crossover studies. These 177 subjects received a total of 533 doses of medication. The incidence of adverse events following exposures of each drug is shown in Table 6.

The most frequently occurring adverse events in healthy subjects following single doses of Kadian™, controlled-release morphine tablets, or immediate-release morphine solution were somnolence, dizziness, headache, and nausea (Table 6). Somnolence and headache each was reported with similar incidence after each formulation (24%-30% for somnolence; 9%-14% for headache); dizziness was reported more often following doses of controlled-release morphine tablets than after Kadian™ or oral morphine solution (30% versus 15% and 9%, respectively); and nausea was reported by more patients after doses of Kadian™ and controlled-release morphine tablets than after oral morphine solution (11% and 22%, respectively versus 2%). Hypothermia (body temperature below normal) and bradycardia were each reported more often following Kadian™ doses than after other morphine formulations; and dry mouth was reported more often following controlled-release morphine tablets and oral morphine solution than after Kadian™ (19% and 15%, respectively versus 3%). Other events were reported in similar incidences following each formulation.

Table 6
Most Frequent Adverse Events by Body System[a]: Studies in Healthy Subjects

	Kadian™	Morphine CR[b]	IR Morphine Solution[c]
Number of subjects	158	43	54
Number of exposures:	425	54	54
Number (%) of events/ number of exposures:[d]			
CENTRAL NERVOUS SYSTEM	161 (38%)	26 (48%)	16 (30%)
Somnolence	106 (25%)	16 (30%)	13 (24%)
Dizziness	59 (14%)	16 (30%)	5 (9%)
Euphoria	15 (4%)	2 (4%)	1 (2%)
Paresthesia	6 (1%)	2 (4%)	1 (2%)
BODY AS A WHOLE	138 (32%)	16 (30%)	15 (28%)
Headache	60 (14%)	6 (11%)	5 (9%)
Hypothermia	59 (14%)	0	0
Dry mouth	12 (3%)	10 (19%)	8 (15%)
Cold symptoms	15 (4%)	1 (2%)	1 (2%)
Fever	11 (3%)	0	0
DIGESTIVE	85 (20%)	20 (37%)	5 (9%)
Nausea	46 (11%)	12 (22%)	1 (2%)
Dyspepsia	23 (5%)	4 (7%)	1 (2%)
Vomiting	13 (3%)	5 (9%)	0
Abdominal pain	14 (3%)	1 (2%)	1 (2%)
Constipation	12 (3%)	2 (4%)	0
CARDIOVASCULAR	72 (17%)	0	1 (2%)
Bradycardia	38 (9%)	0	0
Hypotension	28 (7%)	0	1 (2%)
SKIN & APPENDAGES	35 (8%)	3 (6%)	0
Urticaria	29 (7%)	2 (4%)	0
RESPIRATORY	25 (6%)	2 (4%)	0
SPECIAL SENSES	11 (3%)	5 (9%)	2 (4%)
Eye disorder[e]	7 (2%)	4 (7%)	2 (4%)
Hearing disorder	3 (1%)	2 (4%)	0
METABOLIC & NUTRITIONAL	4 (1%)	0	0
UROGENITAL	1 (<1%)	1 (2%)	0

a Includes individual events occurring in 3% or more of exposures in any group and all body systems with any reported events.

b MS Contin® or MST Continus®

c Immediate-release morphine solution

d Only one occurrence of an event is counted for each exposure.

e Includes blurred vision, double vision, dry eyes, bruised eye, red eyes, eyes watering, difficulty focusing.

ii. Treatment-Related Adverse Events

Adverse events that occurred in healthy subjects and that were considered possibly, probably, or definitely related to treatment are summarized by body system in Table 7. Nearly all occurrences of the most frequently reported treatment-related events (somnolence, dizziness, headache, and nausea) were considered to be at least possibly treatment related; thus, the same comparisons across treatments are seen for treatment-related events as discussed previously for all events.

Table 7
Most Frequent Treatment-Related Adverse Events by Body System[a]: Studies in Healthy Subjects

	Kadian™	Morphine CR[b]	IR Morphine Solution[c]
Number of subjects	158	43	54
Number of exposures:	425	54	54
Number (%) of events/ number of exposures:[d]			
CENTRAL NERVOUS SYSTEM	158 (37%)	26 (48%)	16 (30%)
Somnolence	105 (25%)	16 (30%)	13 (24%)
Dizziness	58 (14%)	16 (30%)	5 (9%)
Euphoria	15 (4%)	2 (4%)	1 (2%)
Paresthesia	5 (1%)	2 (4%)	1 (2%)
BODY AS A WHOLE	59 (14%)	14 (26%)	13 (24%)
Headache	50 (12%)	5 (9%)	4 (7%)
Dry mouth	12 (3%)	10 (19%)	8 (15%)
DIGESTIVE	82 (19%)	20 (37%)	5 (9%)
Nausea	45 (11%)	12 (22%)	1 (2%)
Dyspepsia	23 (5%)	4 (7%)	1 (2%)
Vomiting	12 (3%)	5 (9%)	0
Abdominal pain	13 (3%)	1 (2%)	1 (2%)
Constipation	11 (3%)	2 (4%)	0
CARDIOVASCULAR	21 (5%)	0	1 (2%)
Bradycardia	13 (3%)	0	0
SKIN & APPENDAGES	33 (8%)	3 (6%)	0
Urticaria	29 (7%)	2 (4%)	0
RESPIRATORY	12 (3%)	2 (4%)	0
SPECIAL SENSES	11 (3%)	5 (9%)	2 (4%)
Eye disorder[e]	7 (2%)	4 (7%)	2 (4%)
Hearing disorder	3 (1%)	2 (4%)	0
METABOLIC & NUTRITIONAL	3 (1%)	0	0
UROGENITAL	1 (<1%)	1 (2%)	0

a Includes individual events occurring in 3% or more of exposures in any group and all body systems with any reported events.
b MS Contin® or MST Continus®
c Immediate-release morphine solution
d Only one occurrence of an event is counted for each exposure.
e Includes blurred vision, double vision, dry eyes, bruised eye, red eyes, eyes watering, difficulty focusing.

b. Adverse Events in Patients - Controlled Clinical Trials

Adverse events occurring during the five controlled studies in cancer patients are summarized in this section. Included in the presentations are summaries and analyses of spontaneously reported events; and a summary of elicited morphine-related side effects, the presence and severity of which were recorded by patients using severity rating scales.

(i) All Treatment-Emergent Adverse Events

Treatment-emergent adverse events are summarized by body system in Table 8 (events occurring in at least 3% of patients). In Studies CDD-14556 and MOR-5/92 which were parallel group studies, adverse events observed or reported in Treatment Period 1 were ascribed to the treatment agent for that period. In the crossover studies, the first treatment period in which an adverse event was reported or observed served as the source of the event and was not counted again if it re-occurred in a subsequent treatment period(s). In the crossover studies, each treatment period drug had an equal probability to produce the first occurrence of an adverse event.

Similar proportions of patients reported one or more treatment-emergent adverse events during treatment with Kadian™ and controlled-release morphine tablets (56% and 47%, respectively), and a higher proportion of patients reported treatment-emergent adverse events on immediate-release morphine solution (78%). Central nervous system (CNS) events were the most frequently reported type of event and were reported by fewer patients on Kadian™ and controlled-release morphine tablets than on immediate-release morphine solution (29% and 21%, respectively, versus 51%). Digestive system events were the next most frequently reported and also occurred in a larger proportion of patients on immediate-release morphine solution (55% versus 22% and 17% on Kadian™ and controlled-release morphine tablets, respectively).

Events classified as "Body as a Whole" were reported by a slightly higher proportion of patients on Kadian™ and controlled-release morphine tablets than on the immediate-release formulation (16% and 13%, respectively, versus 7%). Treatment-emergent events related to the skin and appendages were reported by 7% of patients on Kadian™ and no patients on the other formulations. All other types of events were reported in similar frequencies on each formulation.

Table 8
Most Frequent Treatment-Emergent Adverse Events by Body System[a]: Controlled Clinical Trials

	Kadian™	Morphine CR[b]	IR Morphine Solution[c]
Number of patients	227	126	55
Number (%) of patients with one or more events	126 (56%)	59 (47%)	43 (78%)
CENTRAL NERVOUS SYSTEM	66 (29%)	27 (21%)	28 (51%)
Somnolence	21 (9%)	11 (9%)	15 (27%)
Dizziness	13 (6%)	2 (2%)	1 (2%)
Anxiety	12 (5%)	5 (4%)	7 (13%)
Confusion	8 (4%)	1 (1%)	3 (5%)
Anorexia	6 (3%)	7 (6%)	12 (22%)
Dry mouth	6 (3%)	1 (1%)	0
DIGESTIVE	51 (22%)	21 (17%)	30 (55%)
Constipation	20 (9%)	6 (5%)	17 (31%)
Nausea	16 (7%)	3 (2%)	10 (18%)
Vomiting	5 (2%)	6 (5%)	7 (13%)
Abdominal pain	6 (3%)	3 (2%)	1 (2%)
Diarrhea	6 (3%)	2 (2%)	0
BODY AS A WHOLE	36 (16%)	16 (13%)	4 (7%)
Pain	7 (3%)	1 (1%)	1 (2%)
Chest pain	4 (2%)	0	2 (4%)
Infection	2 (1%)	4 (3%)	1 (2%)
Headache	2 (1%)	4 (3%)	0
Disease progression	6 (3%)	1 (1%)	0
RESPIRATORY	17 (7%)	7 (6%)	3 (5%)
Dyspnea	7 (3%)	0	3 (5%)
Respiratory disorder[d]	6 (3%)	1 (1%)	0
SKIN & APPENDAGES	16 (7%)	0	0
Rash	7 (3%)	0	0
METABOLIC & NUTRITIONAL	15 (7%)	5 (4%)	3 (5%)
Peripheral edema	7 (3%)	4 (3%)	2 (4%)
Liver disorder	2 (1%)	0	2 (4%)
CARDIOVASCULAR	11 (5%)	3 (2%)	0
HEMIC & LYMPHATIC	9 (4%)	3 (2%)	2 (4%)
UROGENITAL	7 (3%)	3 (2%)	1 (2%)
MUSCULOSKELETAL	5 (2%)	1 (1%)	3 (5%)
Bone pain	1 (<1%)	0	2 (4%)
SPECIAL SENSES	2 (1%)	4 (3%)	0

[a] Includes individual events occurring in 3% or more of patients in any group and all body systems with any reported events.

[b] MS Contin® or MST Continus®

[c] Immediate-release morphine solution

[d] Includes reported terms of decreased breath sounds (2 patients), respiratory insufficiency (2 patients), wheezing (1 patient), pulmonary infiltrates (1 patient), and bronchi (1 patient).

The most frequently reported individual treatment-emergent adverse events in the controlled studies were somnolence, constipation, nausea, anorexia, anxiety, and vomiting (Table 9). All are side effects typically associated with morphine use, and each was reported by a higher proportion of patients on immediate-release morphine solution than on Kadian™ and controlled-release morphine tablets (27% versus 9% and 9% for somnolence; 31% versus 9% and 5%, respectively, for constipation; 18% versus 7% and 2% for nausea; 22% versus 3% and 6% for anorexia; 13% versus 5% and 4% for anxiety; 13% versus 2% and 5% for vomiting). All other adverse events were infrequent (6% or fewer patients on each formulation) and were reported by similar proportions of patients on each formulation.

Table 9
Incidence of Most Frequent[a] Treatment-Emergent Adverse Events: Controlled Clinical Trials

	Kadian™	Morphine CR[b]	IR Morphine Solution[c]
Number of patients	227	126	55
Number (%) of patients with each event:			
Somnolence	21 (9%)	11 (9%)	15 (27%)
Constipation	20 (9%)	6 (5%)	17 (31%)
Nausea	16 (7%)	3 (2%)	10 (18%)
Anorexia	6 (3%)	7 (6%)	12 (22%)
Anxiety	12 (5%)	5 (4%)	7 (13%)
Vomiting	5 (2%)	6 (5%)	7 (13%)
Dizziness	13 (6%)	2 (2%)	1 (2%)
Confusion	8 (4%)	1 (1%)	3 (5%)
Peripheral edema	7 (3%)	4 (3%)	2 (4%)
Abdominal pain	6 (3%)	3 (2%)	1 (2%)
Dyspnea	7 (3%)	0	3 (5%)
Pain	7 (3%)	1 (1%)	1 (2%)
Diarrhea	6 (3%)	2 (2%)	0
Respiratory disorder[d]	6 (3%)	1 (1%)	0
Infection	2 (1%)	4 (3%)	1 (2%)
Rash	7 (3%)	0	0
Headache	2 (1%)	4 (3%)	0
Chest pain	4 (2%)	0	2 (4%)
Dry mouth	6 (3%)	1 (1%)	0
Disease progression	6 (3%)	1 (1%)	0
Liver disorder	2 (1%)	0	2 (4%)
Bone pain	1 (<1%)	0	2 (4%)

a Events occurring in 3% or more of patients in any group.
b MS Contin® or MST Continus®
c Immediate-release morphine solution
d Includes reported terms of decreased breath sounds, respiratory insufficiency, wheezing, pulmonary infiltrates, and bronchi.

Overall, severe adverse events were reported by 9% of patients during treatment with Kadian™ (20/227 patients) and controlled-release morphine tablets (11/126 patients) and 15% of patients during treatment with oral morphine solution (8/55 patients). Most events reported were mild or moderate in severity. Overall, the most frequently reported severe event was somnolence (2% of patients on Kadian™; 3% on controlled-release morphine tablets, and 2% on oral morphine solution). Severe anorexia was reported by <1% of patients on Kadian™, 1% of patients on controlled-release morphine tablets, and 5% of patients on oral morphine solution. Severe constipation and anxiety were each reported by 4% of patients on oral morphine solution and by 0%-2% of patients on Kadian™ and controlled-release morphine tablets. The incidence of all other severe events was 3% or less on each morphine formulation.

ii. Treatment-Emergent, Treatment-Related Adverse Events

Treatment-emergent adverse events that were classified as possibly, probably, or definitely related to study medication by the investigator[1] were considered treatment-related adverse events; these events are summarized by body system in Table 10.

One or more treatment-related adverse events were reported by 22% of patients during Kadian™ treatment, 16% of patients during treatment with MS Contin® or MST Continus®, and 44% of patients with immediate-release morphine solution. Central nervous system (CNS) events were the most frequently reported type of treatment-related events and were reported by fewer patients on Kadian™ and controlled-release morphine tablets than on immediate-release morphine solution (17% and 12%, respectively, versus 33%). Digestive system events were the next most frequently reported type of treatment-related event and also occurred in a larger proportion of patients on immediate-release morphine solution (38% versus 12% and 8% on Kadian™ and controlled-release morphine tablets, respectively). All other types of treatment-related events were reported by 2% or fewer patients on each treatment.

[1] All other events were considered unrelated or unlikely related to study medication.

The most frequently reported individual treatment-related adverse events were somnolence, constipation, nausea, and anorexia (Table 10), all typical side effects associated with morphine use. Somnolence, constipation and anorexia were reported by a higher proportion of patients on immediate-release morphine solution than on Kadian™ and controlled-release morphine tablets (25% versus 8% and 9%, respectively for somnolence; 29% versus 8% and 5% for constipation; 16% versus 1% and 3% for anorexia; and 11% versus 6% and 2% for nausea). The only other treatment-related events reported by at least 3% of patients were vomiting, dizziness and confusion. Vomiting was reported for slightly more patients on immediate-release morphine solution, and dizziness and confusion were reported for similar proportions of patients on each formulation.

Table 10
Most Frequent Treatment-Related Adverse Events[a] by Body System: Controlled Clinical Trials

	Kadian™	Morphine CR[b]	IR Morphine Solution[c]
Number of patients	227	126	55
Number (%) of patients with one or more events	50 (22%)	20 (16%)	24 (44%)
CENTRAL NERVOUS SYSTEM	39 (17%)	15 (12%)	18 (33%)
Somnolence	18 (8%)	11 (9%)	14 (25%)
Anorexia	3 (1%)	4 (3%)	9 (16%)
Dizziness	7 (3%)	0	0
Confusion	5 (2%)	1 (1%)	2 (4%)
DIGESTIVE	28 (12%)	10 (8%)	21 (38%)
Constipation	19 (8%)	6 (5%)	16 (29%)
Nausea	13 (6%)	2 (2%)	6 (11%)
Vomiting	2 (1%)	4 (3%)	5 (9%)
SKIN & APPENDAGES	5 (2%)	0	0
BODY AS A WHOLE	3 (1%)	1 (1%)	1 (2%)
UROGENITAL	1 (<1%)	1 (1%)	0
SPECIAL SENSES	1 (<1%)	0	0
RESPIRATORY	1 (<1%)	0	0
MUSCULOSKELETAL	1 (<1%)	0	0
METABOLIC & NUTRITIONAL	0	2 (2%)	0

a Includes individual events that occurred in 3% or more of patients in any group and that were considered possibly, probably, or definitely related to study medication, and all body systems with any reported events.
b MS Contin® or MST Continus®
c Immediate-release morphine solution

iii. Analysis of Adverse Event Occurrence Rates

The occurrence rates for frequently reported treatment-emergent adverse events and for body system classifications of events were compared across study treatments (Kadian™ q12h, Kadian™ q24h, controlled-release morphine tablets, and immediate-release morphine solution) to ascertain whether there were any statistically significant differences between the morphine formulations/regimens.

A significant difference across treatment groups was observed for the overall incidence of treatment-emergent adverse events and for central nervous system and digestive system events (Table 11). Results of pairwise comparisons demonstrate that a significantly higher proportion of patients experienced one or more treatment-emergent events or central nervous system events on Kadian™ q12h and on immediate-release morphine solution than on Kadian™ q24h and controlled-release morphine tablets (69% and 78% versus 39% and 47%, respectively, for all adverse events; 38% and 51% versus 18% and 21% for central nervous system events); no significant difference was observed between Kadian™ q12h and immediate-release morphine solution. A significantly higher proportion of patients experienced digestive system events on immediate-release morphine solution than on Kadian™ q12h, Kadian™ q24h, or controlled-release morphine tablets (55% versus 28%, 16%, and 17%, respectively.

Table 11
Analysis of Adverse Events by Body System: Controlled Clinical Trials[c]

Body System	Kadian™ q12h	Kadian™ q24h	Morphine CR[a]	IR Morphine Solution[b]
Number of patients	123	104	126	55
Number (%) of patients with one or more events in any body system:	85 (69%)	41 (39%)	59 (47%)	43 (78%)
CENTRAL NERVOUS SYSTEM	47 (38%)[d]	19 (18%)	27 (21%)	28 (51%)[d]
DIGESTIVE	34 (28%)	17 (16%)	21 (17%)	30 (55%)[e]
BODY AS A WHOLE	25 (20%)	11 (11%)	16 (13%)	4 (7%)
RESPIRATORY	9 (7%)	8 (8%)	7 (6%)	3 (5%)
METABOLIC & NUTRITIONAL	10 (8%)	5 (5%)	5 (4%)	3 (5%)
SKIN & APPENDAGES	12 (10%)	4 (4%)	0	0
HEMIC & LYMPHATIC	4 (3%)	5 (5%)	3 (2%)	2 (4%)
CARDIOVASCULAR	5 (4%)	6 (6%)	3 (2%)	0
UROGENITAL	4 (3%)	3 (3%)	3 (2%)	1 (2%)
MUSCULOSKELETAL	4 (3%)	1 (1%)	1 (1%)	3 (5%)
SPECIAL SENSES	1 (1%)	1 (1%)	4 (3%)	0

a MS Contin® or MST Continus®
b Immediate-release morphine solution
c Analysis performed using SAS® PROC FREQ C-M-H Row Means Test. No adjustment was made for patients who received multiple treatments. For significant ($p \leq 0.05$) between-group findings, pairwise comparisons were performed using Fisher's Exact test, adjusted for multiplicity.
d Pairwise comparisons showed incidences for KADq12h > KADq24h and MCR, and IRMS > KADq24h and MCR ($p \leq 0.032$).
e Pairwise comparisons showed incidences for IRMS > KADq12h, KADq24h, and MCR ($p \leq 0.004$).

A significant difference across treatment groups was observed for the incidence of the most frequently occurring adverse events (somnolence, constipation, anorexia, nausea, anxiety, vomiting, and dizziness; Table 12). Results of pairwise comparisons demonstrate that a significantly higher proportion of patients experienced somnolence, constipation, nausea, and anorexia on immediate-release morphine solution than on Kadian™ q24h or controlled-release morphine tablets, and a significantly higher proportion of patients experienced vomiting on immediate-release morphine solution than on Kadian™ q24h. In addition, the incidence of anorexia was higher on immediate-release morphine solution in comparison with Kadian™ q12h; and the incidence of constipation was higher on Kadian™ q12h than on Kadian™ q24h. For anxiety and dizziness, pairwise comparisons revealed no significant differences between groups.

Table 12
Analysis of Most Frequent[a] Treatment-Emergent Adverse Events: Controlled Clinical Trials[d]

	Kadian™ q12h	Kadian™ q24h	Morphine CR[b]	IR Morphine Solution[c]
Number of patients	123	104	126	55
Number (%) of patients with each event:				
Somnolence	16 (13%)	5 (5%)	11 (9%)	15 (27%)[f]
Constipation	17 (14%)[g]	3 (3%)	6 (5%)	17 (31%)[f]
Nausea	12 (10%)	4 (4%)	3 (2%)	10 (18%)[f]
Anorexia	6 (5%)	0	7 (6%)	12 (22%)[h]
Anxiety	10 (8%)	2 (2%)	5 (4%)	7 (13%)
Vomiting	4 (3%)	1 (1%)	6 (5%)	7 (13%)[i]
Dizziness	10 (8%)	3 (3%)	2 (2%)	1 (2%)
Confusion	5 (4%)	3 (3%)	1 (1%)	3 (5%)
Peripheral edema	6 (5%)	1 (1%)	4 (3%)	2 (4%)
Abdominal pain	2 (2%)	4 (4%)	3 (2%)	1 (2%)
Dyspnea	3 (2%)	4 (4%)	0	3 (5%)
Pain	5 (4%)	2 (2%)	1 (1%)	1 (2%)
Diarrhea	4 (3%)	2 (2%)	2 (2%)	0
Respiratory disorder[e]	4 (3%)	2 (2%)	1 (1%)	0
Infection	1 (1%)	1 (1%)	4 (3%)	1 (2%)
Rash	5 (4%)	2 (2%)	0	0
Headache	1 (1%)	1 (1%)	4 (3%)	0
Chest pain	4 (3%)	0	0	2 (4%)
Dry mouth	4 (3%)	2 (2%)	1 (1%)	0
Disease progression	3 (2%)	3 (3%)	1 (1%)	0
Liver disorder	1 (1%)	1 (1%)	0	2 (4%)
Bone pain	1 (1%)	0	0	2 (4%)
Fever	4 (3%)	1 (1%)	3 (2%)	0
Sweating	5 (4%)	0	3 (2%)	1 (2%)
Asthenia	2 (2%)	3 (3%)	0	0
Accidental injury	1 (1%)	3 (3%)	0	0
Anemia	2 (2%)	3 (3%)	2 (2%)	1 (2%)
Leukopenia	1 (1%)	3 (3%)	1 (1%)	1 (2%)

a Events occurring in 3% or more of patients in any group.
b MS Contin® or MST Continus®
c Immediate-release morphine solution
d Analysis performed using SAS® PROC FREQ C-M-H Row Means Test. No adjustment was made for patients who received multiple treatments. For significant ($p \leq 0.05$) between-group findings, pairwise comparisons were performed using Fisher's Exact test, adjusted for multiplicity.
e Includes reported terms of decreased breath sounds, respiratory insufficiency, wheezing, pulmonary infiltrates, and rhonchi.
f Pairwise comparisons showed incidences for IRMS > KADq24h and MCR ($p \leq 0.034$).
g Pairwise comparisons showed incidences for KADq12h > KADq24h ($p=0.024$).
h Pairwise comparisons showed incidences for IRMS > KADq12h, KADq24h and MCR ($p \leq 0.015$).
i Pairwise comparisons showed incidences for IRMS > KADq24h ($p=0.016$).

c. Deaths, Discontinuations Due to Adverse Experiences, Serious Adverse Experiences, and Potentially Serious Adverse Experiences

Data on all serious adverse events, adverse experiences that resulted in death or discontinuation, and all potentially serious adverse experiences that did not prevent the patient from continuing in the study are reported in this section.

Serious adverse events were considered to include:

- All deaths.
- Life-threatening events.
- Events which were permanently disabling or incapacitating.
- Events which required or prolonged hospitalization.
- Any congenital anomaly or cancer or drug overdose.
- Serious laboratory abnormalities associated with relevant clinical signs or symptoms.

i. Reports from Completed Trials Included in This Submission

Reports of all deaths, discontinuations due to adverse experiences, serious adverse experiences, and potentially serious adverse experiences are presented in the sections to follow.

(1) Deaths

A total of 47 deaths occurred in patients participating in the clinical trials reported in this NDA. None of the reported deaths was attributable to study medication, but rather to disease progression. Of these deaths, 28 occurred while the patient was taking Kadian™, 17 occurred while the patient was taking an IRM formulation, and none occurred while the patient was taking MS Contin®. Eighteen of the 28 deaths occurred while the patient was taking Kadian™ in one of the long-term open-label extension studies. An additional two deaths occurred in patients assigned to the placebo group in Study CDD-14556. These patients were receiving morphine in the form of IRM rescue medication. The number of deaths are listed by study in Table 13.

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Table 13
Deaths Occurring during Clinical Studies

Study	Invest. Pt No.	Gender/Age	Treatment	Days of Treatment
MOB-1/90	09JR	M/65	Kadian™ q24h	24
	25VP	F/66	Kadian™ q12h	4
	27RS	M/50	IRM	13
	16DW	M/70	Kadian™ q12h	15
	02JF	M/61	IRM	20
CDD-14556	01-02Z-C	F/47	Placebo	18
	08-03KLL	M/44	Placebo	36
	06-04BNL	M/68	IRM	1[a]
	08-01DFR	F/59	IRM	6[a]
	25-02I-S	F/52	Kadian™ q24h	20
	28-29CAB	F/58	Kadian™ q24h	6
	39-11NCC	M/57	Kadian™ q24h	6
	15-04WRR	M/74	IRM	4[a]
	23-11TMF	F/23	IRM	11[a]
	24-05DKM	F/27	IRM	3[a]
	29-16WLK	M/68	IRM	5
	35-06DJE	F/70	IRM	14[a]
	35-08D-J	M/63	IRM	5
	39-04DBS	F/64	IRM	8[a]
	23-02WJW	F/62	IRM	15[a]
	25-01FMK	F/66	IRM	10[a]
	17-07RER	M/78	Kadian™ q12h	2
	27-06BOP	F/81	IRM	5[a]
MOR-9/92	19PIL	F/46	Kadian™ q24h	10
	21RDO	M/59	IRM	18
	78DB	M/58	Kadian™ q12h	63
MOBES-8/90	PHM	M/56	IRM	25[a]
	LM	F/47	IRM	8[a]
	03MG	M/70	Kadian™ q12h	7
	78DB	M/58	Kadian™ q12h	63[b]

[a]: Patient not randomized;
[b]: Death occurred during follow-up period.

Table 13 (Cont.)
Deaths Occurring During Clinical Studies

Study	Invest. Pt. No.	Gender/ Age	Treatment	Days of Treatment
MOS 2/91, MOS 3/91, MOR 3/92	KB05	M/56	Kadian™ q12h	240
	BD08	M/50	Kadian™ q12h	120
	WT10	M/64	Kadian™ q12h	150
	LG51	M/68	Kadian™ q12h	210
	CW73	F/68	Kadian™ q12h	Unknown
	KH15	M/66	Kadian™ q12h	30
	WH17	M/49	Kadian™ q12h	180
MOS-1/91	26GD/18	M/49	Kadian™ q24h	20
	07NM/4	F/59	Kadian™ q12h	
	49KP/33	M/47	Kadian™ q12h	84
	01SH/1	M/77	Kadian™ q12h	78
	30KN/22	M/64	Kadian™ q12h	25
	05RH/3	M/70	Kadian™ q24h	35
	28TK	M/56	Kadian™ q12h	18
	RW22	M/78	Kadian™ q12h	90
	IR29	M/78	Kadian™ q12h	90
MOR-5/92	RPAH-05GFH	F/42	Kadian™ q12h	4

(2) Discontinuations Because of Serious Adverse Experiences

During the course of the clinical trial program 16 patients were withdrawn because of serious adverse events. Of the 16 withdrawals due to adverse events, one during Lead-In was possibly related to study drug, one on IRM q4h was related, and three on Kadian™ q12h were related. All other adverse events were unrelated to study medication.

Of the patients withdrawn, 13 were receiving Kapanol®, 3 were receiving IRM, and none were receiving MS Contin®. A list of withdrawals due to serious adverse events by study and patient is presented in Table 14. Where attribution by the investigator to study agents was included in the narratives it has been included in the table below.

Table 14
Patients Who Discontinued Clinical Studies Due to Serious Adverse Events

Study No.	Invest.-Pt.No., Gender/Age	Treatment	Days of Treatment	Event: Relationship to study Medication
MOB 1/90: Open label	40JH, F/61	IRM in Lead-In	2	Abnormal liver function tests, possibly related
	16DWM, M/70	Kadian™ q12h	7	Disease state deterioration, unrelated
	33DH, M/39	IRM q4h	2	Abdominal pain, unrelated
CDD 14556: Double-blind	38-03R-B F/73	Kadian™ q24h	1	Dehydration & hyponatremia, unrelated
	17-07RER M/78	Kadian™ q12h	3	Disorientation & bone fractures, probably related to study agent
	23-08SIM M/66	Kadian™ q12h	5	Hallucinations requiring hospitalization, related
	41-05BWH, M/70	Kadian™ q12h	1	Pneumonia requiring hospitalization, unrelated
MOR 9/92: Double-blind	23DAO , F/55	Kadian™ q24h	7	Shortness of breath due to lung cancer, unrelated
MOBES 8/90: Double-blind	74HMN, M/83	Kadian™ q12h	28*	Anemia, unrelated
	71DH, F/62	Kadian™ q12h	25*	Pseudo-bowel obstruction, unrelated
	04RSW, M/59	Kadian™ q12h	9	Impending spinal cord compression, unrelated
	76RP, M/48	IRM q4h	3	Constipation, related
	07SDD, F/41	Kadian™ q12h	41*	Dyspnea & pleural effusion, unrelated
MOS 1/91: Open-label	50RS M/67	Kadian™ q12h	5	Nausea & vomiting, possibly related
	18JH F/43	Kadian™ q24h	58	Hospitalization for resection of phaeochromocytoma, unrelated
MOS 2/91, MOS 3/91, MOR 3/92: Open-label	HMP3 M/57	Kadian™ q12h	330	Suspected intentional overdose, unrelated

* Adverse event occurred during the extension period.

The serious adverse events reported to be related to one of the study agents were all among the most commonly reported morphine-related side effects.

(3) Serious or Potentially Serious Events

Serious adverse events from all clinical trials were reviewed for patients with serious adverse events who, nonetheless, continued in the study. Fifty-one patients fell into this category. Of this number, only one of the serious adverse events (nausea and vomiting) was related to study agent; this adverse event began during the Lead-In Period and continued through the end of the study which consisted of one week treatment with MS Contin® q12h. The remaining serious adverse events in this category were all disease related.

A tabulation of all patients by study who experienced serious adverse events but continued on the study are presented in Table 15.

Table 15
Patients Who Experienced Serious or Potentially Serious Events in Clinical Studies but Continued on Treatment

Invest-Pt.No.	Gender/Age	Treatment	Onset Day	Event	Relationship to Study Medication	Comments
MOB 1/90: Open-label						
16DW	M/70	Prior to Lead-In	0	Abnormal lab result	Unrelated	Low Hb, transfusion
37JC	M/62	Kadian™ q4h	1	Shortness of breath	Unrelated	Suspected pneumonia
28TK	M/56	Kadian™ q12h	26	Pleural effusion	Unrelated	
47JD	M/73	Kadian™ q24h		Anemia	Unrelated	Low Hb, transfusion
CDD 14556: Double-blind						
08-03 KLL	M/44	IRM q4h	7	Pleural effusion	Unrelated	
05-11 VMS	F/69	Kadian™ q24h	7	Systemic infection	Unrelated	Infection of unknown origin, possible pneumonia beginning during Lead-In
28-03 YCJ	F/53	Kadian™ q24h	6	COPD	Unrelated	
38-09 VFG	F/61	Kadian™ q24h	5	Hypoxia, shortness of breath	Unrelated	Hypoxia required hospitalization
05-21 RDN	M/37	IRM q4h	2	Nausea & dehydration	Unrelated	Nausea due to cisplatin prior to study
05-29 BLK	F/61	Kadian™ q24h	6	Sepsis	Unrelated	Sepsis secondary to impaired immune system
05-34 BRF	M/34	Kadian™ q12h	3	Dehydration	Unrelated	Dehydration probably due to metastasis
24-02 MEP	F/63	Kadian™ q12h	1	Numbness & weakness	Unrelated	Numbness due to bone cancer
28-07 JWB	M/58	Kadian™ q12h	5	Sepsis & neutropenia	Unrelated	Sepsis due to infection of intravenous port
28-14 GWG	M/63	Kadian™ q12h	7	CHF, thrombocytopenia, pleural effusion, pulmonary infiltrates & atelectasis	Unrelated	Preexisting conditions
28-16 CKC	F/39	IRM q4h, during Lead-In	7	Rt. parotid sialoadenitis	Unrelated	
28-30 IMM	F/56	Kadian™ q12h	6	Pleural effusion, respiratory insufficiency & infection	Unrelated	Patient hospitalized for infection which later resolved
14-04 DHO	M/71	MS Contin®	4	Nausea & vomiting	Related	Symptoms occurred throughout lead-in period & treatment periods
28-37 EW	F/39	MS Contin®	3	Pneumothorax	Unrelated	

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Table 15 (Cont'd)
Patients who Experienced Serious or Potentially Serious Events in Clinical Studies But Continued on Treatment

Invest-Pt.No.	Gender/Age	Treatment	Onset Day	Event	Relationship to Study Medication	Comments
CDD 14556: Double-blind						
29-19 LMP	F/76	IRM q4h during Lead-In	2	Hip dislocation	Unrelated	
35-02 CEA	M/63	IRM q4h, during Lead-In	3	Febrile neutropenia & chills	Unrelated	
25-02 IS	F/52	Kadian™ q24h	11	Pain & dehydration	Unrelated	
24-01 RKM	M/57	MS Contin® q12h	4	Deep vein thrombosis & phlebitis	Unrelated	
MOBES 8/90: Double-blind						
05KB	M/68	Kadian™ q12h	63*	Anemia	Unrelated	
73CW	F/67	Kadian™ q12h	84*	Severe cough	Unrelated	Cough was present pre-study
77EL	M/77	Kadian™ q12h	63*	Fractured femur	Unrelated	Fracture due to accidental fall
AF82	M/56	Kadian™ q12h	84*	Increasing pain & urinary incontinence	Unrelated	Dosage of Kadian™ increased from 60 to 110 mg q12h
MOS 1/91: Open-label						
42BG	F/58	Kadian™	3	Dyspnea & central chest pain	Unrelated	Patient hospitalized for bronchoscopy to determine cause
41HW	M/75	Kadian™ q12h	0	Hospitalization & radiotherapy	Unrelated	Radiotherapy for prostate cancer
17WH	M/49	Kadian™ q12h	10	Hemoptysis	Unrelated	
21RW	M/73	Kadian™ q12h	10	Paraplegia	Unrelated	
MOS 2/91, MOS 3/91, MOR 3/92: Open-label						
PV01	M/59	Kadian™ q12h	60	Deep vein thrombosis	Unrelated	
			150	Lymphadenopathy	Unrelated	
WW02	M/76	Kadian™ q12h	150	Abdominal pain, melena & dyspnea	Unrelated	
RW72	M/50	Kadian™ q12h	180	Pleurisy & pain	Unrelated	Patient had cancer of the pleura
		Kadian™ q12h	240	Pleurisy & pain		
GS79	F/54	Kadian™ q12h	180	Malignant breast tumor	Unrelated	
11FA	M/67	Kadian™ q24h	30	Atrial fibrillation & sweating	Unrelated	
DW80	F/43	Kadian™ q12h	60	Exacerbation of pain	Unrelated	

Table 15 (Cont'd)
Patients who Experienced Serious or Potentially Serious Events in Clinical Studies But Continued on Treatment

Invest-Pt.No.	Gender/Age	Treatment	Onset Day	Event	Relationship to Study Medication	Comments
MOS 2/91, MOS 3/91, MOR 3/92: Open-label						
DW80	F/43	Kadian™ q12h	120	Appendicitis	Unrelated	
			150	Appendicitis & exacerbation of pain		
AT81	M/80	Kadian™ q12h	30	Drowsiness & dehydration	Unrelated	
AF82	M/56	Kadian™ q12h	180	Sciatica & exacerbation of back pain	Unrelated	
JH14	F/67	Kadian™ q12h	150	Dyspnea	Unrelated	
WH17	M/49	Kadian™ q12h	30	Hemoptysis	Unrelated	
			90	Constipation	Unrelated	
			180	Paraplegia, dyspnea, pseudo bowel obstruction, poss. lung infection & death	Unrelated	
LG51	M/68	Kadian™ q24h	210	Chest pain & leg weakness	Unrelated	
LD12	M/74	Kadian™ q12h	60	Ankle edema & induration	Unrelated	
RW22	M/78	Kadian™ q12h	60	Respiratory tract infection	Unrelated	
IR29	M/78	Kadian™ q12h	60	Dyspnea	Unrelated	Patient hospitalized on two occasions over a 2-week period
			90	Pleural effusion & death	Unrelated	
			120	Anemia	Unrelated	
MOR 5/92: Open label						
HRH-07-EB	F/68	MS Contin®	4	Deep vein thrombosis & sepsis	Unrelated	Not randomized
RBH-05--AS	M/52	MS Contin®	6	Acute renal failure	Unrelated	Not randomized
RBH-07-SD	F/93	MS Contin®	13	Panic attacks	Unrelated	Not randomized
RAHJ-08-WC	M/42	Kadian™ q24h	10	Urinary retention	Unrelated	
RBH-03-De	M/68	Kadian™ q12h	7	Confusional state	Unrelated	
RAH-06-SM	F/64	Kadian™ q12h	23	Febrile neutropenia	Unrelated	

ii. Reports from Ongoing Trials

Patients who completed a number of the Kadian™ clinical studies were eligible to continue into open label extension studies.

A total of 230 serious adverse experiences have been reported to date. A summary tabulation of these serious adverse events by treatment group is provided in Table 16 for patient deaths, discontinuations, and those who experienced serious adverse events but continued in the study. Narratives for these patients may be found in Appendix E. Additional information will be provided on these studies in the first amendment to be filed to this NDA.

Table 16
Summary Tabulation of Deaths and Withdrawals Due to Serious Adverse Events and Patients Who Experienced Serious Adverse Events but Continued on Study in Ongoing Extension Studies

Study Drug	Deaths	Withdrawals	Continued on Study
Kadian™ q12h	28	34	26
Kadian™ q24 h	28	28	20
Morphine CR q12h	22	23	21

The distribution of deaths, withdrawals due to serious adverse experiences, and patients who continued on study in spite of an adverse experience(s) was similar across all treatment groups since disease progression is the underlying cause of the majority of these events. None of the deaths were treatment related but rather were due to disease progression.

3. Clinical Laboratory Data

Clinical laboratory data were obtained prior to and at the of treatment in crossover studies in healthy subjects and in short-term (crossover and parallel-group) controlled clinical trials in cancer patients; in addition, periodic clinical laboratory evaluations were made during the open-label extension studies in patients. All data from studies in patients were evaluated for clinically significant abnormalities using NCI toxicity grades. For parallel-group studies CCD-14556 and MOR-5/92, summaries of toxicity grades are evaluated by treatment group; for crossover studies, summaries are evaluated by treatment phase (pre-study, post-study, and follow-up) only. For studies in healthy subjects, all laboratory values identified as clinically significant or that warranted follow-up evaluations are identified.

a. Hematologic Data in Cancer Patients

Hematologic data (WBC count, platelet count, hemoglobin, and absolute neutrophil count) from studies in cancer patients were examined for clinically significant abnormalities using NCI toxicity grades. A standard set of normal ranges was used across all studies, and conversion of units was performed where necessary to standardize the data across trials.

i. Hematologic Data from Parallel-Group Trials

All hematologic data from the two parallel-group clinical trials (CCD-14556 and MOR-5/92) were summarized by NCI toxicity grade and treatment group. The distribution of NCI toxicity grades was similar across all treatment groups for all parameters (WBC count, platelet count, hemoglobin, and absolute neutrophil count) evaluated. The incidences of Grade 3 and Grade 4 toxicity were low (<1%-4% for Grade 3 toxicity; 0%-1% for Grade 4 toxicity) for each parameter and treatment group.

In addition to the distribution of all data by NCI toxicity criteria, the number of patients who progressed from one toxicity grade to a higher grade at the end of the parallel-group studies was evaluated by treatment. The distribution of progression in NCI toxicity was similar across treatment groups for each hematologic parameter. The proportion of patients who progressed to Grade 3 toxicity (0%-4%) was low in each treatment group for each parameter. Progression to Grade 4 toxicity occurred for WBC count in one patient (Kadian™ q24h), and for absolute neutrophil count for three patients (2 on Kadian™ q12h and 1 on Kadian™ q24h). All patients who progressed to an increased toxicity grade are identified in Appendix C.11 of the Integrated Summary of Safety (Volume 101).

ii. Hematologic Data from Crossover Trials

Hematology data from the crossover studies in cancer patients (Studies MOB-1/90, MOBES-8/90, MOR-2/92, and MOR-9/92) were summarized by NCI toxicity grade and treatment phase (pre-study, post-study, and follow-up). The distribution of NCI toxicity grades was similar across all treatment phases for WBC count, platelet count, and absolute neutrophil count. A lower incidence of Grade 0 toxicity and a higher incidence of Grade 2 toxicity was seen for hemoglobin post-study relative to the pre-study and follow-up phases. The incidences of Grade 3 and Grade 4 toxicity were very low (0%-2% for Grade 3 toxicity; <1% for Grade 4 toxicity) for each parameter during the crossover and follow-up phases of the studies.

In addition to the distribution of all data by NCI toxicity criteria, the number of patients who progressed from one toxicity grade to a higher grade at the end of the crossover studies was evaluated by treatment. There were no patients who progressed to a Grade 4 toxicity, and only one patient (1%) who progressed to a Grade 3 toxicity (for hemoglobin). The proportion of patients who experienced any progression in toxicity grade was small (≤ 3%) for all parameters except hemoglobin, for which a number of patients progressed to a Grade 1 (28%) or Grade 2 (15%) toxicity. All patients who progressed to an increased toxicity grade are identified in Appendix C.11 of the Integrated Summary of Safety (Volume 101).

b. Serum Chemistry Data in Cancer Patients

Serum chemistry data (bilirubin, SGOT, SGPT, alkaline phosphatase, creatinine, and BUN) from studies in cancer patients were examined for clinically significant abnormalities using NCI or EORTC toxicity grades. A standard set of normal ranges was used across all studies, and conversion of units was performed where necessary to standardize the data across trials.

i. Serum Chemistry Data from Parallel-Group Trials

All serum chemistry data from the two parallel-group clinical trials (CCD-14556 and MOR-5/92) were summarized by NCI toxicity grade and treatment group. The distribution of NCI toxicity grades was similar across all treatment groups for all parameters (alkaline phosphatase, SGOT, SGPT, total bilirubin, creatinine, and BUN) evaluated. The incidences of Grade 3 and Grade 4 toxicity were low (0-1%) for each parameter and treatment group, with the exception of alkaline phosphatase. Nearly half the patients in each treatment group had mildly to severely (Grades 1 to 3) elevated alkaline phosphatase values and one patient had a Grade 4 elevation; these abnormalities are likely related to the patients' underlying cancer with bone metastases.

In addition to the distribution of all data by NCI toxicity criteria, the number of patients who progressed from one toxicity grade to a higher grade at the end of the parallel-group studies was evaluated by treatment. The distribution of progression in NCI toxicity was similar across treatment groups for each serum chemistry parameter. No patients experienced progression to Grade 3 or 4 toxicity levels for SGOT, SGPT, bilirubin, creatinine, or BUN. Two patients, one who received Kadian™ q24h and one who received controlled-release morphine tablets, experienced an increase in alkaline phosphatase to Grade 3 toxicity levels. All patients who progressed to an increased toxicity grade are identified in Appendix C.11 of the Integrated Summary of Safety (Volume 101).

ii. Serum Chemistry Data from Crossover Trials

Serum chemistry data from the crossover studies in cancer patients (Studies MOB-1/90, MOBES-8/90, MOR-2/92, and MOR-9/92) were summarized by NCI toxicity grade and treatment phase (pre-study, post-study, and follow-up). The distribution of NCI toxicity grades was similar across all treatment phases for alkaline phosphatase, SGOT, SGPT, bilirubin, and creatinine. A lower incidence of Grade 0 toxicity and a higher incidence of Grade 1 toxicity was seen for BUN in the follow-up phase relative to the pre-study and post-study phases. The incidences of Grade 3 and Grade 4 toxicity were very low (0%-2% for Grade 3 toxicity; 0%-1% for Grade 4 toxicity) during the crossover and follow-up phases of the studies for each parameter except alkaline phosphatase. During each treatment phase, the incidence of Grade 3 toxicity levels for alkaline phosphatase was 4% to 6% and the incidence of Grade 4 toxicity was <1% to 2%. As mentioned previously, the high levels of alkaline phosphatase seen in these studies is likely related to bone metastases in these cancer patients.

In addition to the distribution of all data by NCI toxicity criteria, the number of patients who progressed from one toxicity grade to a higher grade at the end of the crossover studies was evaluated by treatment. There were no patients who progressed to a Grade 4 toxicity; six patients who progressed to a Grade 3 toxicity (4 for alkaline phosphatase, 1 for SGOT, and 1 for bilirubin) The proportion of patients who experienced any progression in toxicity grade was small (≤ 7%) for all parameters. All patients who progressed to an increased toxicity grade are identified in Appendix C.11 of the Integrated Summary of Safety (Volume 101).

c. Clinically Significant Laboratory Abnormalities in Healthy Subjects

Clinical laboratory assessments (hematology, serum chemistry, and urinalysis) were made at screening and at the end of the study in each of the seven single-dose crossover studies conducted in healthy subjects. Of the 177 subjects treated in these studies, 23 (13%) had one or more abnormalities noted at the end of treatment that were considered clinically significant and/or warranted follow-up. The most frequent type of abnormality was increased liver enzymes (SGOT, SGPT, and/or GGT); these were observed at the end of the study in five subjects, three of whom also had abnormal values obtained prior to entering the study. Decreased neutrophils and increased eosinophils were reported for three subjects each; all other abnormalities were reported for one or two subjects each. In the majority of cases, the abnormalities were resolved on follow-up evaluations conducted 1 to 2 weeks after the end of the study.

4. Adverse Experience Dose-Response Data

a. Treatment-Emergent Adverse Events by Dosage Groups

The incidence of treatment-emergent adverse experiences in controlled clinical trials was examined by daily morphine dose (<120 mg, 120-240 mg, > 240 mg; Table 44). No apparent relationship with daily dose was observed for the overall incidence of treatment-emergent adverse events on any morphine formulation. Among patients who received Kadian™, one or more adverse events were reported by 53% of patients receiving daily doses less than 120 mg, 62% of patients receiving daily doses of 120 to 240 mg, and 50% of patients receiving doses greater than 240 mg. For individual events, there was also little relationship between daily dose of morphine (in any formulation) and the incidence of treatment-emergent adverse events. Among patients who received Kadian™, a slightly higher incidence of nausea was observed with increasing daily dose (4% of patients receiving less than 120 mg/day, 9% of patients receiving 120-240 mg/day, and 13% of patients receiving more than 240 mg/day). No relationship with daily morphine dose and incidence of treatment-emergent nausea was observed for sustained-release morphine tablets, but a higher incidence of vomiting was observed at doses greater than 240 mg than in the lower dose groups (13% versus 3%). In patients receiving controlled-release morphine solution, much higher incidences of nausea, constipation, and somnolence were observed at doses greater than 240 mg than in other dose categories; however, the number of patients receiving high doses of oral morphine solution was too small (n=4) to draw any conclusions regarding dose-response relationships.

Although the overall incidence of treatment-emergent respiratory disorders was small (3% [6/227] of patients receiving Kadian™ and 1% [1/126] of patients receiving controlled-release morphine tablets), a slightly higher incidence of respiratory disorders was observed with increasing dose within the Kadian™ group (1% [1/106] at doses less than 120 mg; 4% [3/81] at doses of 120-240 mg, and 5% [2/40] at doses greater than 240 mg). Examination of data for individual patients and events, however, fails to demonstrate any evidence of a dose-related effect on the respiratory system. All except one of the six patients who experienced respiratory disorders on Kadian™ had lung cancer as their primary tumor type. The individual events that were termed respiratory disorders were as follows, by dose: <120 mg - one patient with decreased breath sounds; 120-240 mg - two patients with respiratory insufficiency and one patient with rhonchi; > 240 mg - one patient with wheezing and one patient with pulmonary infiltrates.

00330

While it is recognised that illicit users will undoubtedly find a method of extracting morphine from Kadian™, it appears that the formulation of Kadian™ may make this process more difficult than for other formulations such as MS Contin®.

4. Conclusions

a. A review of both preclinical and clinical data confirms the established profile of morphine sulfate with respect to physical dependence, development of tolerance and precipitation of a withdrawal syndrome.

b. While physical dependence, tolerance and withdrawal symptoms are observed in patients treated with morphine sulfate for chronic moderate to severe pain, several large studies have confirmed that the risk of addiction in patients is very low. Recent data have confirmed that increases in the total daily dose of morphine in cancer patients are due to progression of the disease rather than tolerance.

c. The abuse liability potential of Kadian™ should be less than that of conventional and other controlled-release formulations of morphine sulfate. The pharmacokinetic profile of Kadian™ demonstrates:

i. slow onset of action;
ii. lower peak plasma morphine levels relative to other morphine formulations;
iii. long duration of action; and,
iv. minimal fluctuations in peak to trough plasma levels of morphine at steady state.

d. Whilst it is almost impossible to prevent the attempted illicit use of morphine-containing preparations, Kadian™ is unlikely to be the morphine formulation of choice for illicit use given that its pharmacokinetic profile is unlikely to produce euphoria or the desired short term effects.

e. The pharmaceutical formulation of Kadian™ means that it is likely to be more difficult to extract the morphine sulfate.

f. When used as directed, Kadian™ provides no greater risk of abuse or addiction in the opioid-naive user than currently available morphine preparations and offers less theoretical risk of abuse due to the formulation and pharmacokinetic profile of Kadian™.

000331

E. Drug Abuse Liability Assessment Summary

NDA Voume 103

Kadian™ is a new formulation of morphine sulfate, a drug which is used as the reference compound for comparison in abuse liability studies of new chemical entities and for which extensive abuse liability data are available. The question to be addressed in the Abuse Liability Assessment for Kadian™, therefore, is not whether there is potential for abuse of morphine sulfate but whether there is a greater likelihood of abuse as a result of the formulation of Kadian™.

The Drug Abuse Liability Assessment Summary section of this application provides a review of the:

- preclinical literature on the abuse liability potential of morphine sulfate;
- clinical literature on the abuse liability potential of morphine sulfate;
- potential for abuse of Kadian™ in comparison to other available morphine formulations in the following situations:

a. therapeutic use in cancer patients;

b. non-therapeutic use by health care providers; and,

c. potential for misuse of the intact and non-intact Kadian™ formulation.

1. <u>Review of preclinical literature on the abuse liability potential of morphine sulfate</u>

Preclinical studies, reviewed by Clouet & Iwatsubo (1975), indicate that daily administration of morphine to rodents, cats, dogs or monkeys by various routes of administration produces tolerance which develops at a rate dependent on the dosage schedule, the interval between doses and the sensitivity of the pharmacological assay. Rothman (1992) suggested that the mechanism underlying morphine tolerance involves the release of anti-opioid peptides which produce tolerance to the effects of morphine and symptoms on withdrawal of morphine.

The development of physical dependence following chronic use of opioid analgesics is a normal pharmacological response, characterized by withdrawal symptoms if treatment is stopped abruptly. Adams & Wooten (1993) suggest that morphine dependence is due to chronic occupation of mu opioid receptors and a quantitative relationship between morphine plasma concentrations (as determined by area under the curve (AUC)) and withdrawal symptoms for a given morphine dose has been demonstrated by Domino *et al* (1987).

A recent study by Gold *et al* (1994) indicated that tolerance and physical dependence to morphine develop over a similar time course.

Preclinical studies by Takamura *et al* (1991) support the development of dependence to morphine in animals implanted with MS Contin® tablets, a controlled-release preparation of morphine sulfate. The degree of dependence was greater than that seen in animals treated with morphine in conventional dose forms, perhaps due to prolonged exposure of morphine receptors.

Correlation of the preclinical findings with clinical data was confirmed by Griffiths & Balster (1979) in abuse potential studies of a range of morphine-like analgesics in humans and monkeys.

2. Review of the clinical literature on the abuse liability potential of morphine sulfate.

Clinical testing for drug abuse liability potential of morphine has included healthy subjects, opioid abusers or ex-addicts, and patients receiving morphine for therapeutic purposes.

While the development of tolerance and physical dependence was confirmed in all populations, several studies in patients with cancer pain have shown that drug abuse and psychological dependence did not occur in this group of patients. The major factor for escalation of drug intake was progression of metastatic disease with increasing severity of pain. (Kanner & Foley (1981); Chapman & Hill (1989); Collin *et al* (1993))

Despite the results of these clinical studies, there are still erroneous physician beliefs and inadequate use of opioid analgesics in the treatment of cancer pain. Portenoy (1993) suggested that concern about tolerance development should never prevent the administration of opioids to patients with cancer pain. Similarly, the development of physical dependence poses no problem as long as patients are warned to avoid an abrupt discontinuation of the drug.

The need for greater education of physicians involved in the care of cancer patients has been addressed by Jacox *et al* (1994) in the Clinical Practice Guideline for the Management of Cancer Pain issued by the Agency for Health Care Policy and Research, United States Department of Health and Human Services.

3. Potential for abuse of Kadian™

The pharmacokinetics of morphine following single doses of Kadian™are an important consideration in assessing the abuse and dependence potential for therapeutic and non-therapeutic use.

Following administration of single doses of Kadian™, peak morphine levels in plasma (C_{max}) are much lower than those seen after immediate release morphine sulfate solution (x1/4) or MS Contin® (x1/2) and are achieved after longer time periods (t_{max}) than recorded for immediate release morphine sulfate solution (x8) and MS Contin® (x3-4). Therefore the initial rapid, high peak levels of morphine sulfate, possibly leading to euphoria, will not be achieved following a dose of Kadian™.

According to the FDA Draft Guidelines for Abuse Liability Assessment (1990), the characteristics of slow onset and long duration of action are likely to provide a formulation with lower abuse liability.

The pharmacokinetic profile of Kadian™ suggests that, in its marketed presentation, Kadian™ may have a lower abuse liability potential due to its slow onset of action, prolonged duration of action and minimal fluctuations in peak to trough morphine plasma concentrations. This may make Kadian™ less attractive to abusers than either immediate-release morphine sulfate solution or a marketed controlled-release tablet formulation of morphine sulfate (MST Continus® or MS Contin®).

a. Therapeutic use in patients with cancer pain.

The draft US labeling for Kadian™ states that:

> "Kadian™ is indicated for the management of pain where treatment with an opioid analgesic is indicated for more than a few days.
>
> Kadian™ was developed for use in patients with chronic pain who require repeated dosing with potent opioid analgesics, and has been tested in patients with pain due to a variety of malignant conditions. Kadian™ has not been tested as an analgesic for the treatment of acute pain or in the postoperative setting and is not recommended for such use."

This will in most cases relate to patients with cancer pain.

As discussed earlier, patients treated for chronic cancer pain may be physically dependent on morphine without becoming addicted to it. (Kanner & Foley (1981); Chapman & Hill (1989); Collin *et al* (1993); Portenoy (1993)). Warfield (1993) further states that tolerance to the analgesic effect of morphine is not a significant problem in the treatment of cancer pain. Several studies have shown that patients with stable disease (malignant or non-malignant in origin) can be maintained on the same dose of analgesic for extremely long periods.

The draft U.S. labeling for Kadian™ recognises the possibility of development of physical dependence, tolerance and the withdrawal syndrome and includes appropriate wording under the heading of 'Drug Abuse and Dependence'.

Kadian™, when used as directed, represents no greater risk of abuse or addiction in the opioid naive user with chronic moderate to severe pain, than other current forms of morphine therapy.

b. Non-therapeutic use in Health Care Providers

While the medical use of morphine preparations in patients with cancer pain has not shown a risk of addiction, the use of morphine by health care providers or other illicit use by the general public is associated with a high risk of physical and psychological drug dependence. The choice of formulation of morphine used by addicts is generally that which can be injected intravenously, ie. morphine sulfate solutions.

Kadian™ is less likely to be abused by health care providers and illicit users for the following reasons:

i. slow onset of action;
ii. lower peak plasma morphine levels than equivalent doses of other formulations of morphine;
iii. long duration of action; and,
iv. minimal fluctuations in peak to trough plasma levels of morphine at steady state.

c. Potential misuse of the intact and non-intact formulation of Kadian™

Publications by Crews & Denson (1990) and Bloor & Smalldridge (1990) indicated that MS Contin® tablets have the potential for diversion to illicit use through the extraction and intravenous injection of the morphine from this controlled-release formulation.

The unique pharmaceutical formulation of Kadian™ offers some protection from extraction of morphine sulfate for intravenous use by illicit users. Kadian™ 20, 50, 100 mg capsules contain identical polymer-coated sustained-released pellets of morphine sulfate. This polymer coating delays the extraction of morphine sulfate from Kadian™. Dissolution testing with Kadian™ capsules in water showed that after 8 hours only 30% of the morphine has been released (Alexander (1992)).

While it is recognised that illicit users will undoubtedly find a method of extracting morphine from Kadian™, it appears that the formulation of Kadian™ may make this process more difficult than for other formulations such as MS Contin®.

4. Conclusions

a. A review of both preclinical and clinical data confirms the established profile of morphine sulfate with respect to physical dependence, development of tolerance and precipitation of a withdrawal syndrome.

b. While physical dependence, tolerance and withdrawal symptoms are observed in patients treated with morphine sulfate for chronic moderate to severe pain, several large studies have confirmed that the risk of addiction in patients is very low. Recent data have confirmed that increases in the total daily dose of morphine in cancer patients are due to progression of the disease rather than tolerance.

c. The abuse liability potential of Kadian™ should be less than that of conventional and other controlled-release formulations of morphine sulfate. The pharmacokinetic profile of Kadian™ demonstrates:

   i. slow onset of action;
   ii. lower peak plasma morphine levels relative to other morphine formulations;
   iii. long duration of action; and,
   iv. minimal fluctuations in peak to trough plasma levels of morphine at steady state.

d. Whilst it is almost impossible to prevent the attempted illicit use of morphine-containing preparations, Kadian™ is unlikely to be the morphine formulation of choice for illicit use given that its pharmacokinetic profile is unlikely to produce euphoria or the desired short term effects.

e. The pharmaceutical formulation of Kadian™ means that it is likely to be more difficult to extract the morphine sulfate.

f. When used as directed, Kadian™ provides no greater risk of abuse or addiction in the opioid-naive user than currently available morphine preparations and offers less theoretical risk of abuse due to the formulation and pharmacokinetic profile of Kadian™.

APPLICATION SUMMARY

8. DISCUSSION OF BENEFIT/RISK RELATIONSHIP AND PROPOSED POST-MARKETING STUDIES NDA Volume 59

There is a great unmet medical need for effective strong analgesic drugs with limited side effects. The patients with the greatest need are those with chronic cancer pain. Up to 50% of cancer patients undergoing active treatment and up to 90% with advanced disease have pain severe enough to require treatment with analgesics, but in 40-50% of patients their pain is not adequately relieved (1). The World Health Organisation has recognised that cancer pain is commonly under treated and frequently neglected, and has made the control of pain and symptoms one of the priorities of its cancer control programme (2).

In the United States alone, it is estimated that 510,000 cancer deaths occurred in 1990 (3). Of these patients, 60-80% had severe pain during the terminal phase of the illness (4). A recent assessment of the unmet analgesic needs in cancer patients has indicated that at least 70% of dying cancer patients have pain that interferes with quality of life and function (5). It is clear that poorly controlled pain is an important factor that detracts from quality of life at any stage of disease and has far-reaching consequences for patients and their families.

Effective drug therapy is the cornerstone of cancer pain management. The training of healthcare professionals in the management of cancer pain using the three-step analgesic ladder and the proper availability of effective opioid analgesics are two elements of the World Health Organisation's strategy for the development of national cancer pain relief programmes. Opioid analgesics, the major class of analgesics used in the management of moderate to severe chronic cancer pain, are effective, easily titrated to analgesic effect and have a favourable benefit-to-risk ratio. The Clinical Development program for Kadian™ has demonstrated its particular benefits:

- It is as effective as other oral controlled-released opioid analgesics.
- The frequency of administration is reduced compared to other oral morphine products, consequently improving patient compliance and convenience and reducing care-giver time.
- Being an opioid agonist, without antagonist properties, it is as effective as other opioids and the increasing doses that may be required to control increasing pain are only limited by intolerable side effects.
- Clinical efficacy studies with Kadian™ have demonstrated that it is an effective strong analgesic drug product.

The risks associated with treatment with Kadian™ are similar to those for other morphine products. However, the total risk profile can be divided in to "real risks" and "perceived risks".

The real risk of treatment with oral morphine products are the risks associated with side effects. The most common are nausea and vomiting, sedation and mental clouding, constipation and respiratory depression. Constipation is a common effect of opioid treatment and requires, in most cases, prophylactic treatment with laxatives. Nausea and vomiting are generally transient and associated with the initiation of opioid treatment in opioid-naive patients. Sedation and mental clouding occur in a small percentage of patients. Respiratory depression is a very low risk because pain is a strong driver of respiration. This side effect has not been reported in any Kadian™ clinical studies.

Other opioid side effects such as dry mouth, urinary retention, pruritus, dysphoria and euphoria are infrequent but have been included in the product labelling.

Treatment with oral morphine for chronic pain management also carries certain perceived risks that have been dispelled in recent years. It is now well accepted that tolerance to morphine therapy is not a clinical concern. Increasing doses of morphine are required because of disease progression. Similarly, patients do not remain intolerant to adverse symptoms such as sedation with continued use of morphine. When the pain has been relieved and morphine dosing is tapered slowly, patients do not remain physically dependent on the drug and do not experience withdrawal. Patients treated with opioids for cancer pain do not become "addicted".

Education programmes that are consistent with the World Health Organisation Cancer Pain initiatives are assisting in educating healthcare workers who are involved in the management of patients with cancer pain. Kadian™ has demonstrated a high benefit-low risk profile in the management of chronic cancer pain when used in accordance with the product labelling.

PROPOSED POST-MARKETING STUDIES — NDA Volume 103

Two post-marketing studies are currently proposed for Kadian™: a Labelling Validation or Comprehension Study to be conducted during NDA review, and an efficacy and safety study in children.

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Labelling Validation Study

This study is to be conducted at the request of the Principal Medical Reviewer for Kadian™ in the FDA's Pilot Drug Evaluation Staff.

There are certain restrictions on characteristics of the patient population as a consequence of inclusion/exclusion criteria in studies conducted up to the end of Phase III. These restrictions may affect the safety and efficacy profiles of a drug when it is used in novel clinical settings or under less well-controlled conditions post-marketing. Thus, Phase III studies may not accurately predict the post-approval safety of a drug in general clinical use.

The objective of a labelling validation study is:

- to test the clinician's comprehension of the proposed labelling; and
- to develop a dataset representing the safety of the drug in actual clinical use.

Study Outline

- open-label study
- n = 100 to 150 patients with moderate to severe chronic pain
- 10 to 15 investigator sites in the US

The physicians are to prescribe Kadian™ according to their interpretation of the close-to-final labelling. Patients will receive Kadian™ according to the physician's interpretation of the instructions in the labelling.

Data will be collected on the following: patient diagnosis, previous medication for pain, other diseases, dose, interval and duration of treatment with Kadian™, adverse events, comparison with drugs of the same class, effectiveness of pain control and physician comprehension of the labelling.

The study will start 3Q 1995 and will recruit over 6 to 9 months.

Efficacy and Safety Study in Children

Faulding anticipates undertaking a clinical development program for Kadian™ in children because no controlled-release morphine formulations have a labelling claim for use in this population. An efficacy and safety study, with limited pharmacokinetics, is proposed in children to obtain a claim for the use of Kadian™ in this patient population.

Proposed Study Outline

Double-blind, randomized, cross-over design comparing Kadian™ administered every 12 hours with Kadian™ administered every 24 hours for 7 ± 2 days.

n = 24 patients with moderate to severe chronic cancer pain.

The study will be conducted at investigator sites in the US.

The total daily dose of morphine required for pain control will be determined during a lead-in phase in which patients are stabilised on immediate-release morphine formulations.

Patients will then receive both Kadian™ every 12 hours and Kadian™ every 24 hours, in a randomized fashion, each given for 7 ± 2 days.

Efficacy will be determined by time to first dose of rescue medication and amount of rescue medication over the 24 hour period on day 7(±2), pain scores, and patient and investigator global assessments of pain.

Safety will be assessed by morphine-related side effects, adverse events, clinical laboratory assessments and vital signs.

A subset of patients will have blood taken over a 24 hour period at steady state for pharmacokinetic analysis of morphine, morphine-3-glucuronide and morphine-6-glucuronide.

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