From: Nathalie Leitch
Sent: Thursday, October 15, 2009 3:26 PM
To: 'Balogh, Christine'; 'Birtchet, Alan'; Terrence Fullem
Cc: 'Mignon, Paul'; 'Levy, Richard , (inVentiv Communications)'
Subject: RE: inVentiv Follow Up
Attachments: StatGram.pdf; Effect of alcohol on KADIAN pk.pdf

Hi – the sales team has two additional pieces currently available; the first describes the benefits of Kadian versus generic MS Contin and the second describes the KADIAN capsules story and key benefits of the product. Two additional pieces, a conversion guide and visual aid, are currently being printed and will be available to the field very shortly. I will send you copies of these pieces.

We are also looking to leverage results from a study that Alpharma did which looked at the effects of alcohol on Kadian pk. I've attached a copy of an article re this study that was published in the Journal of Pain along with a statgram that Alpharma sent out summarizing the results of the study. Kadian is the only product in the category that has done such a study and which can make the "no dose dumping in the presence of alcohol" claim – we think this is a significant differentiator and would like to incorporate this message into the overall Kadian safety message.

Nathalie

Nathalie Leitch
Assoc Director, US Hsptl & CA Mkt

actavis
creating value in pharmaceuticals

Actavis
60 Columbia Rd. Bldg B *t* 973-889-6968 @ NLeitch@actavis.com
Morristown , NJ 07960 United States *w* www.actavis.com
Internal VoIP number *t* 125 6968

From: Balogh, Christine [mailto:cbalogh@consultCHS.com]
Sent: Thursday, October 15, 2009 5:55 PM
To: Nathalie Leitch; Birtchet, Alan; Terrence Fullem
Cc: Mignon, Paul; Levy, Richard , (inVentiv Communications)
Subject: RE: inVentiv Follow Up

Nathalie - I'll work with our Med Ed group Selva to create a proposal and we'll be sure to address your question regarding expected ROI, timing and cost for the program. It would be helpful to get the previous materials utilized by Alpharma (slide kit etc.) to understand what may need to be updated.

Alan did manage to get his hands on a set of materials currently utilized by the field (sales aid/PI, Co-Pay assistance brochures and the Kadian MOA CD). Are there any materials we're missing?

We can definitely aim to reconvene the week of the 26th - let me check calendars and we'll get back to you with proposed dates/times.

PLAINTIFFS TRIAL EXHIBIT
P-16060_00001

Best Regards,

Tina

Christine Balogh
Vice President
Integrated Client Development
inVentiv Advance Insights
500 Atrium Drive
Somerset, NJ 08873
w 732-537-4884
c 732-620-0681
f: 866-908-7320
cbalogh@inventivhealth.com
www.inventivhealth.com

From: Nathalie Leitch [mailto:NLeitch@actavis.com]
Sent: Thursday, October 15, 2009 4:32 PM
To: Birtchet, Alan; Terrence Fullem
Cc: Mignon, Paul; Balogh, Christine
Subject: RE: inVentiv Follow Up

Hi -

Thanks for your note, Alan. It was good to see you, Tina and Paul last week and helpful to walk through some ideas with you for providing ongoing support for Kadian.

Mike and Mark are interested in creating a speakers program. I will track down the materials used by Alpharma and will forward to you once located. Given where we're at in the product life-cycle, our decision to move forward with such a program will be based on time and cost to implement as well as an understanding of expected market impact. It would be helpful if, along with proposed budget and timeline, you could provide us with additional information relating to expected ROI. I recognize that the impact may best be described qualitatively as the objective of this program would in part be to re-establish a connection with KOL and high volume writers; fine. Any information that you can provide to help us understand benefits of implementing such a program would be appreciated.

I have taken a quick look through the report that you sent – thank you. There is some good information here. I will give some thought to specific metrics that we may want to monitor more closely in the future.

Could we aim to reconvene for a follow-up meeting during the week of October 26th? Let me know.

Thanks again,

Nathalie

Nathalie Leitch
Assoc Director, US Hsptl & CA Mkt

Actavis
60 Columbia Rd. Bldg B t 973-889-6968 @ NLeitch@actavis.com
Morristown , NJ 07960 United States w www.actavis.com
Internal VoIP number t 125 6968

From: Birtchet, Alan [mailto:ABirtchet@inVentivhealth.com]
Sent: Tuesday, October 13, 2009 2:40 PM
To: Nathalie Leitch; Terrence Fullem
Cc: Mignon, Paul; Balogh, Christine
Subject: RE: inVentiv Follow Up

Nathalie and Terry,
It was good to see you last week to discuss the Kadian opportunity. I've enjoyed the interaction with the sales force and managers to date. I share their (and your) enthusiasm about the opportunity with Kadian.

In recent conversations, Mark and Mike seem particularly supportive of creating a speakers program. I know Tina has had conversations with folks from our Communications team and MedConference to formulate strategy on how we could collaborate to accomplish this efficiently. Is it possible to get a copy of the old Alpharma speaker slide kit to consider how best top update and repurpose this material? This would be helpful as we develop a proposal for the initiative.

I've talked with our Analysis and Reporting (A&R) team regarding creation of reports based on data supplied by the sales force. We had discussions at the initiation of the project about the need for in-depth reporting of activity at which time it seemed to not be critical. There are some data available which was used to create the attached. These reports are among a standard suite of reports that we can provide. As you'll remember, no activity reports were included as deliverables for the team at launch.
I want to point out a few things:
1) There are no call detail records. This caused an issue on the reports where no calls were appearing. We made the assumption that all contacts were Kadian calls which I expect is valid. If we intend to generate activity reports moving forward, we may want to provide more direction to the field around reporting.
2) We don't have specialty or decile information on all Targets so you will see a number of Targets in the XX (decile) group and OTH (Other) specialty group. If we get segmentation information we can re-run the reports after we update the missing information.
3) The call goals given were 12 for deciles 6 and above and 8 for decile 5 and below. A&R assumed these were quarterly goals. We can re-run this report to reflect changes to frequency goals.
3) Overall Reach is at 66.2%. The % of calls to targets is over 99%. Frequency is trending for the most part from highest decile down to lowest in terms of times called. Calls per day is low at 4.7.
These reports provide examples of what can be generated. If you want to see specific activity metrics in the future, we can recreate reports accordingly. If data are not available, we may give different direction to the field to ensure we capture elements we believe are important.

Let's try to schedule a follow up meeting to discuss the issues/opportunities we identified. Specifically, we agreed to consider:

- how a speaker program could be developed and events conducted.
- how materials could be updated and some developed to refresh the Kadian sales message and supplement a 'safety' message, including the issue of alcohol toxicity.
- how a mail campaign could be initiated quickly
- what analytics could be done quickly to assess promotional effect and whether additional sales people could have positive ROI

I look forward to meeting again soon.
Regards
Alan

From: Balogh, Christine
Sent: Wednesday, October 07, 2009 12:10 PM
To: 'Nathalie Leitch'; Terrence Fullem
Cc: Mignon, Paul; Birtchet, Alan
Subject: inVentiv Follow Up

Nathalie / Terry- It was great to see you both yesterday

As a follow-up on a few of the Communications initiatives (speaker programs, updating slide kits, updated selling materials, mass letter to pharmacy/md's regarding Cardinal stocking/safety message), it would be helpful to get a copy of the current materials so we can make some recommendations. I met with Rich Levy (my counterpart in Communications) this morning who used to be agency of record for Kadian when it was at Alpharma - so he's got in-depth knowledge of the product. He will also pull in one of our agencies to outline ideas/costs.

On my end, I'll work on the analytics proposal to outline costs around our sales optimization to determine where it may make sense to add more representatives. It would be helpful to understand the number of targets you are hitting with your telesales program as well. I can incorporate this into our analysis as a separate line item so you can choose whether you'd like to include in the analytics.

As a next step, it would be ideal to get a date on the calendar and we'll plan to come back to walk you through our recommendations and proposals.

Best Regards,

Tina

Christine Balogh
Vice President
Integrated Client Development
inVentiv Advance Insights
500 Atrium Drive
Somerset, NJ 08873
w 732-537-4884
c 732-620-0681
f: 866-908-7320
cbalogh@inventivhealth.com
www.inventivhealth.com

ALPHARMA
Pharmaceuticals

June 8, 2007

UPS OVERNIGHT COURIER

Food and Drug Administration
Center for Drug Evaluation & Research
Division of Drug Marketing, Advertising, & Communications
5901-B Ammendale Road
Beltsville, MD 20705

RE: NDA # 20-616, KADIAN® (morphine sulfate extended-release) Capsules, 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg

Dear Colleague:

Alpharma Pharmaceuticals LLC is hereby submitting, in duplicate, the following promotional material(s) for KADIAN® (morphine sulfate extended-release) Capsules:

StatGram KADIAN® ETOH Study Results "Dear Doctor" Letter
Job Code: KADI7SG0001

Coupon Request Letter
Job Code: KADI7D0060E

If you have any questions relating to this submission, please do not hesitate to contact the undersigned at (732) 465-3670.

Sincerely,

ALPHARMA PHARMACEUTICALS LLC

Diane B. Salerno for

Charlene Salmorin
Associate Director, Labeling & Registrations

/cs
Enclosures

Regulatory Affairs Department
One New England Avenue, Piscataway, NJ 08854
Telephone: 732-465-3631
Facsimile: 732-465-3724

Note: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. DATE SUBMITTED: 6/8/2007

2 LABEL REVIEW NO. *(Biologics)*

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 2008
See OMB Statement on Reverse Part 1

3. NDA/ANDA/AADA OR BLA/PLA/PMA
Number: 20-616
Single product ☒ Multiple products ☐
For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.

4. PROPRIETARY NAME	5. ESTABLISHED NAME	6. PACKAGE INSERT DATE and ID NO *(Latest final printing labeling)*	7. MANUFACTURER NAME:
KADIAN	Morphine Sulfate E-R Caps Prod. Code No. N/A	October 2006 Part #40-9064	N/A License No. N/A *(Biologics)*

FDA/CBER USE ONLY

REVIEWED BY:	DATE	RETURNED BY:	DATE

8. **ADVERTISMENT / PROMOTIONAL LABLEING MATERIALS**

Please check one or both: ☒ Professional ☐ Consumer

Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS:
PLT	6/5/2007	StatGram: KADIAN ETOH Study Results "Dear Doctor" Letter Job Code: KADI7SG0001	N/A	

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Charlene Salmorin, Associate Director, Labeling & Reg.

10. SIGNATURE OF RESPONSIBLE OFFICIAL
Diane B. Salmorin for Charlene Salmorin

11. APPLICANT'S RETURN ADDRESS
One New England Avenue
Piscataway, NJ 08854

12. RESPONSIBLE OFFICIAL'S
a. PHONE NO.
(732) 465-3670
b. FAX NO.
(732) 465-3724

13. BIOLOGICAL PRODUCTS: *(Check One)*
☐ Part I/Draft ☐ Part II/Final

FORM FDA 2253 (10/05) PREVIOUS EDITION IS OBSOLETE. PSC Media Arts (301) 443-1090 EF

Note: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. DATE SUBMITTED: 6/8/2007

2 LABEL REVIEW NO. *(Biologics)*

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 2008
See OMB Statement on Reverse Part 1

3. NDA/ANDA/AADA OR BLA/PLA/PMA
Number: 20-616
Single product ☒ Multiple products ☐
For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.

4. PROPRIETARY NAME	5. ESTABLISHED NAME	6. PACKAGE INSERT DATE and ID NO *(Latest final printing labeling)*	7. MANUFACTURER NAME:
KADIAN	Morphine Sulfate E-R Caps Prod. Code No. N/A	October 2006 Part #40-9064	N/A License No. N/A *(Biologics)*

FDA/CBER USE ONLY

REVIEWED BY:	DATE	RETURNED BY:	DATE

8. **ADVERTISMENT / PROMOTIONAL LABLEING MATERIALS**

Please check one or both: ☐ Professional ☒ Consumer

Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS:
CDM	6/6/2007	Coupon Request Letter Job Code: KADI7D0060E	N/A	

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Charlene Salmorin, Associate Director, Labeling & Reg.

10. SIGNATURE OF RESPONSIBLE OFFICIAL
Jeanne B. Salerno for Charlene Salmorin

11. APPLICANT'S RETURN ADDRESS
One New England Avenue
Piscataway, NJ 08854

12. RESPONSIBLE OFFICIAL'S
a. PHONE NO.
(732) 465-3670
b. FAX NO.
(732) 465-3724

13. BIOLOGICAL PRODUCTS: *(Check One)*
☐ Part I/Draft ☐ Part II/Final

FORM FDA 2253 (10/05) PREVIOUS EDITION IS OBSOLETE. PSC Media Arts (301) 443-1090 EF

Important Prescribing Information

STAT GRAM®

June 2007

ALPHARMA Pharmaceuticals

Dr. John Q. Sample
123 Any Street
Suite 456
Anytown, US 12345-6789

KADIAN® (morphine sulfate extended-release) Capsules
HEALTHCARE PROFESSIONAL LETTER

Dear Healthcare Professional:

Alpharma Pharmaceuticals LLC has conducted an alcohol-formulation interaction study with KADIAN® (morphine sulfate extended-release) Capsules to determine if the concomitant administration of alcohol would accelerate the release of morphine sulfate from KADIAN® capsules. This study, as well as its review by the Food and Drug Administration (FDA), has now been completed. **The results of this study indicate that the extended-release properties of KADIAN® capsules are well-maintained – even in the presence of a significant quantity and concentration of alcohol, and that there is not an interaction between the KADIAN® capsule formulation and alcohol when administered concomitantly.** The following is a summary of the study and its results.

STUDY DESCRIPTION

This was an open-label, randomized, pharmacokinetic, single-dose, 3-way crossover study conducted under fasted and fed conditions in 32 healthy adult male volunteers to assess whether alcohol interferes with the extended-release characteristics of the KADIAN® capsule formulation. The primary endpoints were the mean ratios of area under the curve (AUC), mean ratios of maximum serum concentration (C_{max}), and median time to maximum concentration (T_{max}) of morphine in the KADIAN® and alcohol arms in the fasted and fed states, as compared to the reference arm of KADIAN® capsules and water in a fasted state. The study population was comprised of healthy (opioid-naive), non-smoking, males, aged 21 to 40 years old with a history of moderate alcohol consumption (at least 7-21 alcoholic drinks per week). The study was performed as a 3-way crossover; each subject was either fed a standard high-fat meal (1000 calories) 30 minutes before dosing administration or fasted for a minimum of 10 hours. As a safety precaution, at 12 hours and 2 hours prior to the dosing, subjects were given a 50 mg dose of naltrexone (an

ALPHARMA Pharmaceuticals
Alpharma Pharmaceuticals LLC, One New England Avenue, Piscataway, NJ 08854
Tel: 732-465-3600 – www.alpharma.com

opioid antagonist) to block the effects of the morphine sulfate. At time=0 minutes, subjects were given a single dose of 100 mg KADIAN® and a total of 8 ounces of 80-proof (40%) alcohol over a period of not more than 20 minutes (8 ounces of water for the reference arm). Morphine serum levels were measured over the next 48 hours.

Data were analyzed in two ways, including and excluding subjects who vomited within the 12-hour dosing interval. The results from both analyses showed that the ratios for morphine (AUC) and (C_{max}) for subjects given KADIAN® capsules and alcohol in a fed and fasted state relative to subjects given KADIAN® capsules with water in a fasted state were bio-equivalent[1].

The study showed that:

- Mean serum morphine concentrations of KADIAN® 100 mg capsules co-ingested with 8 ounces of 40% ethanol fasted and fed were bioequivalent to KADIAN® taken without alcohol.
- The mean serum morphine concentration-time profiles following alcohol ingestion in the fasted and fed conditions were consistent with an extended-release formulation.
- The median (T_{max}), 8 hours, was the same for all 3 treatments.

NEW KADIAN® CAPSULE STRENGTHS

Alpharma would also like to inform you that we have received approval from the FDA for both the 200 mg strength of KADIAN®, which is now available, and the 10 mg strength which will be available in September 2007. The new 200 mg strength KADIAN® capsule, as with the 100 mg capsule, should be used in opioid-tolerant patients only.

SAFETY CONSIDERATIONS[2]

KADIAN® capsules are an extended-release 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® capsules contain an opioid agonist which is a Schedule II controlled substance. KADIAN® has an abuse liability similar to other opioid analgesics. 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.
- Serious adverse reactions that may be associated with KADIAN® therapy in clinical use are those observed with other oral opioid analgesics and include respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock.

ALPHARMA
Pharmaceuticals
Alpharma Pharmaceuticals LLC, One New England Avenue, Piscataway, NJ 08854
Tel: 732-465-3600 – www.alpharma.com

- Patients who do not have a proven tolerance to opioids should be started only on the 10 mg or 20 mg strength, and usually increased at a rate not greater than 20 mg every other day. KADIAN® 100 mg and 200 mg capsules are for use in opioid-tolerant patients only.
- KADIAN® capsules are to be swallowed whole and are not to be chewed, dissolved, or crushed. Taking chewed, dissolved, or crushed KADIAN® capsules or pellets leads to rapid release and absorption of a potentially fatal dose of morphine.

The co-ingestion of alcohol with KADIAN® capsules is not recommended. All opioids, including KADIAN® capsules, may be expected to have additive effects and potentially serious outcomes when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Patient safety is our highest priority at Alpharma Pharmaceuticals, and we are committed to providing healthcare professionals with information to appropriately prescribe KADIAN® capsules. We believe this information is valuable for you in your assessment of KADIAN® capsules, and we look forward to educating you and your patients about the appropriate use of KADIAN® for moderate-to-severe chronic pain. For further information, please visit www.KADIAN.com or call 1-877-4KADIAN.

Sincerely,

Stephen Sun, MD
Senior Director, Medical Affairs
Alpharma Pharmaceuticals LLC

Enclosures and References:

1. Study Summary: *The effect of the co-ingestion of alcohol on the pharmacokinetics of KADIAN® (morphine sulfate extended-release) Capsules.* Alpharma Pharmaceuticals LLC, Piscataway, NJ [KAD17D0018, February 2007].
2. KADIAN® [prescribing information]. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

ALPHARMA.
Pharmaceuticals
Alpharma Pharmaceuticals LLC, One New England Avenue, Piscataway, NJ 08854
Tel: 732-465-3600 – www.alpharma.com

The effect of the co-ingestion of alcohol on the pharmacokinetics of KADIAN® (morphine sulfate extended-release) Capsules

The objective of this study was to evaluate the potential for a formulation interaction between KADIAN® capsules and alcohol when both are co-ingested under fasted or fed conditions compared to KADIAN® with water under fasted conditions

An open-label, randomized, single-dose, 3-way crossover pharmacokinetic drug interaction study under fasted and fed conditions between KADIAN® 100 mg extended-release capsules and alcohol conducted in thirty-two (32) healthy adult male subjects

The subjects were randomized in a crossover design into 3 arms to receive: KADIAN® 100 mg with 8 ounces of 40% ethanol (ETOH) fasted, KADIAN® 100 mg with 8 ounces of 40% ethanol fed, and KADIAN® 100 mg with 8 ounces of water fasted. There was a 7-day washout between each arm

50 mg oral Naltrexone Hydrochloride (an opioid antagonist) was administered 12 and 2 hours prior to each treatment to counteract the effects of morphine

The first analysis (Figure 1) includes all subjects who completed ***any arm*** in the study

- The serum morphine time-released profile remained similar among the three arms (KADIAN® and water compared to KADIAN® and alcohol fast/fed)

The second analysis (Figure 2) excluded subjects who vomited during the 12-hour dosing interval

- Eleven subjects in the KADIAN® with alcohol fasted arm vomited (therefore, n=16)
- Three of the eleven subjects also vomited in the KADIAN® with alcohol fed arm (therefore, n=22)
- No subjects vomited after taking KADIAN® and water (therefore, n=26)

The serum morphine profile following co-administration of KADIAN® 100 mg and 40% alcohol does not appear to be different from the profile following KADIAN® and water in either analysis

Figure 1. **Mean Serum Morphine Concentration (All Subjects Who Completed Any Arm)**

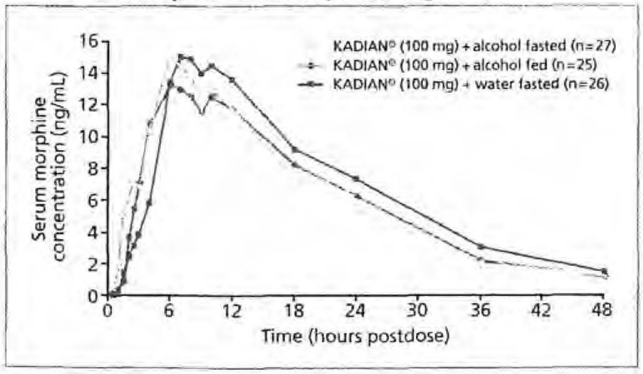
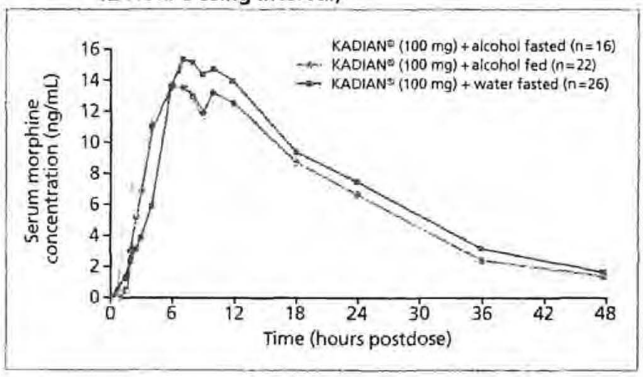


Figure 2. **Mean Serum Morphine Concentration (Excluding Subjects With Emesis Within the 12-Hour Dosing Interval)**



KADIAN®
Morphine Sulfate Extended-Release Capsules
20 mg 30 mg 50 mg 60 mg 80 mg 100 mg

The effect of the co-ingestion of alcohol on the pharmacokinetics of KADIAN® (morphine sulfate extended-release) Capsules

The analysis includes 26 subjects who had completed at least one KADIAN® with alcohol arm and the KADIAN® with water arm.

Ratios of Mean Results (%)

	KADIAN®+ETOH (Fasted)/KADIAN®+H_2O	KADIAN®+ETOH (Fed)/KADIAN®+H_2O
C_{MAX} (ng/mL)	102.3%	98.0%
AUC (ng·hr/mL)	89.1%	89.7%

All values were within the upper and lower bioequivalence confidence interval

The median T_{MAX} for all arms of the study was approximately 8.0 hours

Of the 32 subjects included in the safety analysis, 27 (84%) experienced at least one adverse event (AE) possibly or probably related to the drug administration. Most of the AEs were mild to moderate and one was severe. There were no serious AEs and all AEs were resolved before the end of the study

7 patients discontinued prior to completing all treatment arms (1 due to failed drug test, 5 due to AEs, 1 due to family issues)

KADIAN® capsules co-ingested with 8 ounces of 40% ethanol fasted and fed resulted in mean serum morphine concentrations that were bioequivalent to KADIAN® taken without alcohol

KADIAN® 100 mg capsules co-ingested with 8 ounces of 40% ethanol fasted and fed resulted in mean AUC and peak morphine concentrations consistent with an extended-release formulation

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® capsules contain an opioid agonist which is a Schedule II controlled substance. KADIAN® has an abuse liability similar to other opioid analgesics. 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

Serious adverse reactions that may be associated with KADIAN® therapy in clinical use are those observed with other oral opioid analgesics and include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock

Patients who do not have a proven tolerance to opioids should be started only on the 20 mg strength, and usually increased at a rate not greater than 20 mg every other day. KADIAN® 100 mg capsules are for use in opioid-tolerant patients only

KADIAN® capsules are to be swallowed whole and are not to be chewed, dissolved, or crushed. Taking chewed, dissolved, or crushed KADIAN® capsules or pellets leads to rapid release and absorption of a potentially fatal dose of morphine

The co-ingestion of alcohol with KADIAN® is not recommended

For further information, please visit www.KADIAN.com or call 1-877-4KADIAN

Reference: Data on file. Alpharma Branded Products Division, Piscataway, NJ.

Please see accompanying complete Prescribing Information.

ALPHARMA
Branded Products Division

KADI7D0018 February 2007 Printed in USA

KADIAN®
Morphine Sulfate Extended-Release Capsules
20 mg 30 mg 50 mg 60 mg 80 mg 100 mg

The mean adult plasma clearance is about 20-30 mL/minute/kg. The effective terminal half-life of morphine after IV administration is reported to be approximately 2.0 hours. Longer plasma sampling in some studies suggests a longer terminal half-life of morphine of about 15 hours.

Special Populations

Geriatric: The elderly may have increased sensitivity to morphine and may achieve higher and more variable serum levels than younger patients. In adults, the duration of analgesia increases progressively with age, though the degree of analgesia remains unchanged. KADIAN® pharmacokinetics have not been investigated in elderly patients (>65 years) although such patients were included in the clinical studies.

Nursing Mothers: Morphine is excreted in the maternal milk, and the milk to plasma morphine AUC ratio is about 2.5:1. The amount of morphine received by the infant depends on the maternal plasma concentration, amount of milk ingested by the infant, and the extent of first pass metabolism.

Pediatric: Infants under 1 month of age have a prolonged elimination half-life and decreased clearance relative to older infants and pediatric patients. The clearance of morphine and its elimination half-life begin to approach adult values by the second month of life. Pediatric patients old enough to take capsules should have pharmacokinetic parameters similar to adults dosed on a per kilogram basis (see **PRECAUTIONS - Pediatric Use**).

Gender: No meaningful differences between male and female patients were demonstrated in the analysis of the pharmacokinetic data from clinical studies.

Race: Pharmacokinetic differences due to race may exist. Chinese subjects given intravenous morphine in one study had a higher clearance when compared to caucasian subjects (1852 ± 116 mL/min versus 1495 ± 80 mL/min).

Hepatic Failure: The pharmacokinetics of morphine were found to be significantly altered in individuals with alcoholic cirrhosis. The clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these patients indicating a decrease in metabolic activity.

Renal Insufficiency: The pharmacokinetics of morphine are altered in renal failure patients. AUC is increased and clearance is decreased. The metabolites, M3G and M6G accumulate several fold in renal failure patients compared with healthy subjects.

Drug-Drug Interactions: The known drug interactions involving morphine are pharmacodynamic, not pharmacokinetic (see **PRECAUTIONS - Drug Interactions**).

INDICATIONS AND USAGE

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 (see **CLINICAL PHARMACOLOGY**).

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

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. (See American Pain Society guidelines.)

CONTRAINDICATIONS

KADIAN® is contraindicated in patients with a known hypersensitivity to morphine, morphine salts or any of the capsule components, or in any situation where opioids are contraindicated. This includes in patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute or severe bronchial asthma or hypercarbia.

KADIAN® is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

KADIAN® Capsules are to be swallowed whole and are not to be chewed, crushed, or dissolved. Taking chewed, crushed, or dissolved KADIAN® Capsules leads to rapid release and absorption of a potentially fatal dose of morphine.

KADIAN® 100 mg and 200 mg Capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. This capsule strength may cause fatal respiratory depression when ingested or administered to patients who are not previously exposed to opioids.

Care should be taken in the prescribing of this capsule strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

KADIAN® contains morphine an opioid agonist and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Morphine 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.

Abuse of KADIAN® by crushing, chewing, snorting or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND DEPENDENCE**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

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).

KADIAN® 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 (e.g. severe kyphoscoliosis), 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. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

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. KADIAN® 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® may cause severe hypotension. There is an added risk to individuals 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 and syncope 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.

Interactions with other CNS Depressants

KADIAN® should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result.

40-8064

KADIAN®
Morphine Sulfate
Extended-Release Capsules

Revised — October 2006

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.

Other

Although extremely rare, cases of anaphylaxis have been reported.

PRECAUTIONS

General

KADIAN® is intended for use in patients who require continuous, around-the-clock opioid analgesia for an extended period of time. As with any potent opioid, it is critical to adjust the dosing regimen for KADIAN® for each patient, 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**.

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.

Selection of patients for treatment with KADIAN® should be governed by the same principles that apply to the use of any potent opioid analgesics. Specifically, the increased risks associated with its use in the following populations should be considered: the elderly or debilitated and those with severe impairment of hepatic, pulmonary, or renal function; hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychosis; prostatic hypertrophy, or urethral stricture; acute alcoholism; delirium tremens; kyphoscoliosis; or inability to swallow.

The administration of KADIAN® may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

KADIAN® may aggravate pre-existing convulsions in patients with convulsive disorders.

Cordotomy

Patients taking KADIAN® who are scheduled for cordotomy or other interruption of pain transmission pathways should have KADIAN® ceased 24 hours prior to the procedure and the pain controlled by parenteral short-acting opioids. In addition, the post-procedure titration of analgesics for such patients should be individualized to avoid either oversedation or withdrawal syndromes.

Use in Pancreatic/Biliary Tract Disease

KADIAN® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

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; myxedema; 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 and delirium tremens, and convulsive disorders.

Driving and Operating Machinery

KADIAN® 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 KADIAN® with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol (see **Drug Interactions**).

Information for Patients

If clinically advisable, patients receiving KADIAN®, or their caregivers should be given the following information by the physician, nurse, or pharmacist:

1. Patients should be advised that KADIAN® contains morphine and should be taken only as directed.
2. Patients should be advised that KADIAN® capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternately, KADIAN® capsules may be opened and the entire contents sprinkled on a small amount of apple sauce immediately prior to ingestion. KADIAN® capsules or the contents of the capsules must not be chewed or crushed due to a risk of fatal overdose.
3. Patients should be advised that KADIAN® 100 mg and 200 mg Capsules are for use only in opioid-tolerant patients. Special care must be taken to avoid accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, as such unsupervised use may have severe, even fatal, consequences.
4. Patients should be advised that the dose of KADIAN® should not be adjusted without consulting the prescribing health care provider.
5. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
6. Patients should be advised that KADIAN® may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on KADIAN® or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected.
7. Patients should be advised that KADIAN® should not be taken with alcohol or other CNS depressants (sleeping medication, tranquilizers) except by the orders of the prescribing healthcare provider because dangerous additive effects may occur resulting in serious injury or death.
8. Women of childbearing potential who become or are planning to become pregnant, should consult their prescribing healthcare provider prior to initiating or continuing therapy with KADIAN®.
9. Patients should be advised that if they have been receiving treatment with KADIAN® for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the KADIAN® dose, rather than

abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their prescribing healthcare provider should provide a dose schedule to accomplish a gradual discontinuation of the medication.

10. Patients should be advised that KADIAN® is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
11. Patients should be advised that severe constipation could occur as a result of taking KADIAN® and appropriate laxatives, stool softeners and other appropriate treatments should be initiated from the beginning of opioid therapy.
12. Patients should be instructed to keep KADIAN® in a secure place out of the reach of children. When KADIAN® is no longer needed, the unused capsules should be destroyed by flushing down the toilet.

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, antiemetics, 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: KADIAN® may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression.

Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as KADIAN®. In this situation, *mixed agonist/antagonist* analgesics may reduce the analgesic effect of KADIAN® and/or may precipitate withdrawal symptoms in these patients.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion and *significant depression of respiration or coma.* KADIAN® should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

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

Diuretics: *Morphine can reduce 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.

Carcinogenicity/Mutagenicity/Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of morphine have not been conducted. There are no reports of carcinogenic effects in humans. *In vitro* studies have reported that morphine is non-mutagenic in the Ames test with *Salmonella*, and induces chromosomal aberrations in human leukocytes and ethal mutation induction in *Drosophila*. Morphine was found to be mutagenic *in vitro* in human T-cells, increasing the DNA fragmentation. *In vivo*, morphine was mutagenic in the mouse micronucleus test and induced chromosomal aberrations in spermatids and murine lymphocytes. *Chronic opioid abusers (e.g., heroin abusers) and their offspring display higher rates of chromosomal damage. However, the rates of chromosomal abnormalities were similar in nonexposed individuals and in heroin users enrolled in long term opioid maintenance programs.*

Pregnancy

Teratogenic Effects (Pregnancy Category C)

Teratogenic effects of morphine have been reported in the animal literature. High parental doses during the second trimester were teratogenic in neurological, soft and skeletal tissue. The abnormalities included encephalopathy and axial skeletal fusions. These doses were often maternally toxic and were 0.3 or 3-fold the maximum recommended human dose (MRHD) on a mg/m² basis. The relative contribution of morphine-induced maternal hypoxia and malnutrition, each of which can be teratogenic, has not been clearly defined. Treatment of male rats with approximately 3-fold the MRHD for 10 days prior to mating decreased litter size and viability.

Nonteratogenic Effects

Morphine given subcutaneously, at non-maternally toxic doses, to rats during the third trimester with approximately 0.15-fold the MRHD caused reversible reductions in brain and spinal cord volume, and testes size and body weight in the offspring, and decreased fertility in female offspring. The offspring of rats and hamsters treated orally or intraperitoneally throughout pregnancy with 0.04- to 0.3-fold the MRHD of morphine have demonstrated delayed growth, motor and sexual maturation and decreased male fertility. Chronic morphine exposure of fetal animals resulted in mild withdrawal, altered reflex and motor cell development, and altered responsiveness to morphine that persisted into adulthood.

There are no well-controlled studies of chronic in utero exposure to morphine sulfate in human subjects. However, uncontrolled retrospective studies of human neonates chronically exposed to other opioids in utero demonstrated reduced brain volume which normalized over the first month of life. Infants born to opioid-abusing mothers are more often small for gestational age, have a decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome. KADIAN® should only be used during pregnancy if the need for strong opioid analgesia justifies the maternal risk to the fetus.

Labor and Delivery

KADIAN® is not recommended for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. *However, this effect is not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor. Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression.* A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate.

Neonatal Withdrawal Syndrome

Chronic maternal use of opiates or opioids during pregnancy exposes the fetus. The newborn may experience subsequent neonatal withdrawal syndrome (NWS). Manifestations of NWS include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The onset, duration, and severity of the disorder differ based on such factors as the addictive drug used, time and amount of mother's last dose, and *rate of elimination of the drug from the newborn. Approaches* to the treatment of this syndrome have included supportive care and, when indicated, drugs such as paregoric or phenobarbital.

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. Because of the potential for adverse reactions in nursing infants from KADIAN®, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety of KADIAN®, both the entire capsule and the pellets sprinkled on apple sauce, have not been directly investigated in pediatric patients below the age of 18 years. The range of doses available is not suitable for the treatment of very young pediatric patients or those who are not old enough to take capsules safely. The apple sauce sprinkling method is not an appropriate alternative for these patients.

Geriatric Use

Clinical studies of KADIAN® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly *patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of* decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS:

Serious adverse reactions that may be associated with KADIAN® therapy in clinical use are those observed with other opioid analgesics and include: respiratory depression, respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock (see **OVERDOSAGE, WARNINGS**).

The less severe adverse events seen on initiation of therapy with KADIAN® are also typical opioid side effects. These events are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent of these include drowsiness, dizziness, constipation and nausea. In many cases, the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large rapid swings in plasma concentrations of the opioid. Many of *these adverse events will cease or decrease as KADIAN® therapy is continued and some degree of tolerance is developed, but others may be expected to remain troublesome throughout therapy.*

Management of Excessive Drowsiness

Most patients receiving KADIAN® will experience initial drowsiness. This usually disappears within 3-5 days and is not a cause of concern unless it is excessive, or accompanied by unsteadiness or confusion. Dizziness and unsteadiness may be associated with postural hypotension, particularly in elderly or debilitated patients, and has been associated with syncope and falls in non-tolerant patients started on opioids.

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 level (especially in older patients), disease severity and the patient's general condition.

The dosage should be adjusted according to individual needs, but additional care should be used in the selection of initial doses for the elderly patient, the cachectic or gravely ill patient, or in patients not already *familiar with narcotic analgesic medications to prevent excessive sedation at the onset of treatment.*

Management of Nausea and Vomiting

Nausea and vomiting are common after single doses of KADIAN® or as an early undesirable effect of chronic opioid therapy. The prescription of a suitable antiemetic should be considered, with the awareness that sedation *may result (see* **Drug Interactions**). 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, such as KADIAN®, on a chronic basis. Some patients, particularly elderly, debilitated or bedridden patients may become impacted. Tolerance does not usually develop for the constipating effects of opioids. Patients must be cautioned accordingly and laxatives, softeners and other appropriate treatments should be used prophylactically from the beginning of opioid therapy.

Adverse Events Probably Related to KADIAN® Administration

In clinical studies in patients with chronic cancer pain the most common adverse events reported by patients at least once during therapy were drowsiness (9%), constipation (9%), nausea (7%), dizziness (6%), and anxiety (6%). Other less common side effects expected from KADIAN® or seen in less than 3% of patients in the clinical studies were:

Body as a Whole: Asthenia, accidental injury, fever, pain, chest pain, headache, diaphoresis, chills, flu *syndrome, back pain, malaise, withdrawal syndrome*

Cardiovascular: Tachycardia, atrial fibrillation, hypotension, hypertension, palpitation, bradycardia, syncope

Central Nervous System: Confusion, dry mouth, anxiety, abnormal thinking, abnormal dreams, euphoria, *depression, tremor*, loss of concentration, insomnia, amnesia, paresthesia, agitation, vertigo, hot drop, ataxia, hypesthesia, slurred speech, hallucinations, vasodilation, amblyopia, apathy, seizures, myoclonus

Endocrine: Hyponatremia due to inappropriate ADH secretion, gynecomastia

Gastrointestinal: Vomiting, anorexia, dysphagia, hypertonia, diarrhea, abdominal pain, stomach ache, dyspepsia, *gastro-esophageal reflux*, delayed gastric emptying, biliary colic

Hemic & Lymphatic: Anemia, leukopenia, thrombocytopenia

Metabolic & Nutritional: Peripheral edema, hypovitaminosis, edema

Musculoskeletal: Back pain, bone pain, arthralgia

Respiratory: Hiccup, *rhinitis, atelectasis, asthma, hypoxia, dyspnea, respiratory incompetency*, voice alteration, depressed cough reflex, non-cardiogenic pulmonary edema

Skin and Appendages: Rash, decubitus ulcer, pruritus, skin flush

Special Senses: Amblyopia, conjunctivitis, miosis, diplopia, vision abnormalities, otalgia

Urogenital: *Urinary abnormality, amenorrhea*, urinary retention, urinary frequency, reduced libido, reduced potency, prolonged labor

Post-marketing Adverse Events Probably Related to KADIAN®

The safety of KADIAN® has been evaluated in a randomized, prospective, open-label, 4-week treatment period, post-marketing study consisting of 1418 patients ages 18-85 with chronic, non-malignant pain (e.g., back pain, osteoarthritis, neuropathic pain). No control arm was included in this study. The most common adverse events reported at least once during therapy were constipation (12%), nausea (9%) and somnolence (3%). Other less common side effects occurring in less than 3% of patients were vomiting, pruritus, dizziness, sedation, dry mouth, headache, fatigue and rash.

DRUG ABUSE AND DEPENDENCE:

KADIAN® is a mu-agonist opioid with an abuse liability similar to other opioid agonists and is a Schedule II controlled substance. KADIAN® and other opioids used in analgesia can be abused and are subject to criminal diversion.

KADIAN® is an opioid with an approved use in the management of *addiction disorders. Its proper usage in* individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite *harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is* common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and insistence to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in *all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by* misuse for non-medical purposes, often in combination with other psychoactive substances. KADIAN®, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

KADIAN® is intended for oral use only. Abuse of chewed, crushed, or dissolved capsules or pellets poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. Due to the presence of talc as one of the excipients in capsules, parenteral abuse can be expected to result in local tissue *necrosis, infection, pulmonary granulomas, and* increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

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, pulmonary edema, bradycardia, hypotension and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

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 to remove unabsorbed drug when an extended-release formulation such as KADIAN® has been taken. Care should be taken to secure the airway during attempting treatment by gastric emptying or activated charcoal.

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

The pure opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression which

results from opioid overdose. Since the duration of reversal would be expected to be less than the duration of action of KADIAN®, 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 24 hours after administration and the management of an overdose should be monitored accordingly. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be given as directed by the manufacturer of the product.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Such agents 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 opioid 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. The severity of the withdrawal produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist should be reserved for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

DOSAGE AND ADMINISTRATION

KADIAN® may be administered once or twice daily.

KADIAN® capsules should be swallowed whole. The pellets in KADIAN® capsules should not be chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine.

Alternatively, KADIAN® capsules may be administered as a sprinkle on apple sauce or through a 16 french gastrostomy tube (see Alternative Methods of Administration section).

The 100 mg and 200 mg capsules are for use only in opioid-tolerant patients.

KADIAN® is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain), or for pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in these settings have not been established.

KADIAN® is only indicated for post-operative 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.

Patients who are already receiving KADIAN® Capsules as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention.

Initiating Therapy with KADIAN® Capsules

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring.

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. (Note: potency estimates may vary with the route of administration);
3) the patient's degree of opioid experience and 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.

Care should be taken to use low initial doses of KADIAN® in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see PRECAUTIONS).

During periods of changing analgesic requirements including initial titration, frequent communication is recommended between physician, other members of the healthcare team, the patient, and the caregiver/family.

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®

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). KADIAN® should not be given more frequently than every 12 hours.

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

KADIAN® can be administered to patients previously receiving treatment with parenteral morphine or other opioids. 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 provide rescue medication, than to overestimate and manage an adverse event. The following general points should be considered:

1. Parenteral to Oral Morphine Ratio: It may take anywhere from 2-6 mg of oral morphine to provide analgesia equivalent to 1 mg of parenteral morphine. A dose of oral morphine three times the daily parenteral morphine requirement may be sufficient in chronic use settings.
2. Other Parenteral or Oral Opioids to Oral Morphine Sulfate: There is lack of systematic evidence bearing on these types of analgesic substitutions. Therefore, specific recommendations are not possible. Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate. In general, it is safest to give half of the estimated daily morphine demand as the initial dose, and to manage inadequate analgesia by supplementation with immediate-release morphine. (See discussion which follows.)

The first dose of KADIAN® may be taken with the last dose of any immediate-release (short-acting) opioid medication due to the long delay until the peak effect after administration of KADIAN®.

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 an extended-release morphine, it is ordinarily advisable to begin treatment using an immediate-release morphine formulation.

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 Alpharma Branded Products Division Inc. 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-opioid medications (NSAIDs and 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.

KADIAN® should be started by administering one-half of the estimated total daily oral morphine dose every 12 hours (twice-a-day) or by administering the total daily oral morphine dose every 24 hours (once-a-day). The dose should be titrated no more frequently than every other day to allow the patient to stabilize 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 a short-acting analgesic. 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.

Patients who do not have a proven tolerance to opioids should be started only on the 20 mg strength, and usually should be increased 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.

Alternative Methods of Administration

In a study of healthy volunteers, KADIAN® pellets sprinkled over apple sauce were found to be bioequivalent to KADIAN® capsules swallowed whole with apple sauce under fasting conditions. Other foods have not been tested. Patients who have difficulty swallowing whole capsules or tablets may benefit from the alternative method of administration.

1) Sprinkle the pellets onto a small amount of apple sauce. Apple sauce should be room temperature or cooler.
2) The patient must be cautioned not to chew the pellets which could result in the immediate release of a potentially dangerous, even fatal dose of morphine.
3) Use immediately.
4) Rinse mouth to ensure all pellets have been swallowed.
5) Patients should consume entire portion and should not divide apple sauce into separate doses.

The entire capsule contents may alternatively be administered through a 16 French gastrostomy tube.

1) Flush the gastrostomy tube with water to ensure that it is open.
2) Sprinkle the KADIAN® Pellets into 10 mL of water.
3) Use a swirling motion to pour the pellets and water into the gastrostomy tube through a funnel.
4) Rinse the beaker with a further 10 mL of water and pour this into the funnel.
5) Repeat rinsing until all pellets remain in the beaker.

THE ADMINISTRATION OF KADIAN® PELLETS THROUGH A NASOGASTRIC TUBE SHOULD NOT BE ATTEMPTED.

Considerations in the Adjustment of Dosing Regimens

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, if 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 a 12 hour 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 12 hours.

Cessation of Therapy

When the patient no longer requires therapy with KADIAN® capsules, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from KADIAN® to Other Extended-Release Oral Morphine Formulations

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

Conversion from KADIAN® to Parenteral Opioids

When converting a patient from KADIAN® to parenteral opioids, it is best to calculate an equivalent parenteral dose, and then initiate treatment at half of this calculated value. For example, to estimate the required 24 hour dose of parenteral morphine for a patient taking KADIAN®, one would take the 24 hour KADIAN® dose, divide by an oral to parenteral conversion ratio of 3, divide the estimated 24 hour parenteral dose into six divided doses (for a four hour dosing interval), then halve this dose as an initial trial.

For example, to estimate the required parenteral morphine dose for a patient taking 360 mg of KADIAN® a day, divide the 360 mg daily oral morphine dose by a conversion ratio of 1 mg of parenteral morphine for every 3 mg of oral morphine. The estimated 120 mg daily parenteral requirement is then divided into six 20 mg doses, and half of this, or 10 mg, is then given every 4 hours as an initial trial dose.

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.

Safety and Handling

KADIAN® Capsules contain morphine sulfate which is a controlled substance under Schedule II of the Controlled Substances Act. Morphine, like all opioids, is liable to diversion and misuse and should be handled accordingly. Patients and their families should be instructed to flush any KADIAN® capsules that are no longer needed.

KADIAN® may be targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

KADIAN® consists of closed hard gelatin capsules containing polymer coated morphine sulfate pellets that pose no known handling risk to health care workers. KADIAN® Capsules 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 extended-release pellets of morphine sulfate and are available in seven dose strengths:

20 mg size 4 capsule, yellow opaque cap printed with KADIAN and yellow opaque body printed with 20 mg. Capsules are supplied in bottles of 100 (NDC 63857-322-11).

30 mg size 4 capsule, blue violet opaque cap printed with KADIAN and blue violet opaque body printed with 30 mg. Capsules are supplied in bottles of 100 (NDC 63857-325-11).

50 mg size 2 capsule, blue opaque cap printed with KADIAN and blue opaque body printed with 50 mg. Capsules are supplied in bottles of 100 (NDC 63857-323-11).

60 mg size 1 capsule, pink opaque cap printed with KADIAN and pink opaque body printed with 60 mg. Capsules are supplied in bottles of 100 (NDC 63857-326-11).

80 mg size 0 capsule, light orange opaque cap printed with KADIAN and light orange opaque body printed with 80 mg. Capsules are supplied in bottles of 100 (NDC 63857-412-11).

100 mg size 0 capsule, green opaque cap printed with KADIAN and green opaque body printed with 100 mg. Capsules are supplied in bottles of 100 (NDC 63857-324-11).

200 mg size 0 capsule, light brown opaque cap printed with KADIAN and light brown opaque body printed with 200 mg. Capsules are supplied in bottles of 100 (NDC 63857-377-11).

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Protect from light and moisture.

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

CAUTION: DEA Order Form Required.

KADIAN® is a registered trademark.
KADIAN is a trademark owned by Alpharma Branded Products Division Inc.

Manufactured for: **Alpharma Branded Products Division Inc.**
One New England Avenue
Piscataway, NJ 08854
By: Actavis Elizabeth LLC
200 Elmora Avenue
Elizabeth, NJ 07207 USA

KADIAN®

Morphine Sulfate Extended-Release Capsules

CII

KADIAN® 20 mg Capsules
KADIAN® 30 mg Capsules
KADIAN® 50 mg Capsules
KADIAN® 60 mg Capsules
KADIAN® 80 mg Capsules
KADIAN® 100 mg Capsules
KADIAN® 200 mg Capsules

Rx only

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.

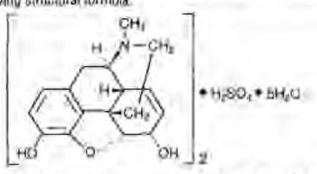
KADIAN® Capsules are NOT for use as a prn analgesic.

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.

DESCRIPTION

KADIAN® (morphine sulfate) capsules are an opioid analgesic supplied in 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg strengths for oral administration.

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



Morphine sulfate is an odorless, 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_a is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4).

Each KADIAN® extended-release capsule contains either 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, or 200 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: hypromellose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, corn starch, and sucrose. The capsule shells contain gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and black ink. D&C yellow #10 (20 mg), FD&C red #3, FD&C blue #1 (30 mg), D&C red #28, FD&C red #40, FD&C blue #1 (50 mg), D&C red #28, FD&C red #40, FD&C blue #1 (60 mg), FD&C blue #1, FD&C red #40, FD&C yellow #6 (80 mg), D&C yellow #10, FD&C blue #1 (100 mg), black iron oxide, yellow iron oxide, red iron oxide (200 mg).

CLINICAL PHARMACOLOGY

Morphine is a natural product that is the prototype for the class of natural and synthetic opioid 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 located throughout the body. Morphine acts as a pure agonist, binding with and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

Effects on the Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis). The precise mechanism of the analgesic action is unknown. However, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects. Morphine produces respiratory depression by direct action on brainstem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brainstem respiratory centers to increases in carbon dioxide tension, and to 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 opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis, rather than miosis may be seen with worsening hypoxia in the setting of KADIAN® overdose (See **OVERDOSAGE**).

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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 the sphincter of Oddi.

Effects on the Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Release of histamine may be induced by morphine and can contribute to opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating.

Pharmacodynamics

Plasma Level-Analgesia Relationships

In any particular patient, both analgesic effects and plasma morphine concentrations are related to the morphine dose.

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. The effective dose in opioid-tolerant patients may be 10-50 times as great (or greater) than the appropriate dose for opioid-naive individuals. Dosages of morphine should be chosen and must be titrated on the basis of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

For any fixed dose and dosing interval, KADIAN® will have, at steady state, a lower C_{max} and a higher C_{min} than conventional morphine.

Pharmacokinetics

KADIAN® capsules contain polymer coated extended-release pellets of morphine sulfate that release morphine significantly more slowly than from conventional oral preparations. KADIAN® activity is primarily due to morphine. One metabolite, morphine-6-glucuronide, has been shown to have analgesic activity, but does not readily cross the blood brain barrier.

Following oral administration of morphine, the extent of absorption is essentially the same for immediate or extended 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 in the gastrointestinal tract.

Elimination of morphine is primarily via hepatic metabolism to glucuronide metabolites (55 to 65%) which are then renally excreted. The terminal half-life of morphine is 2 to 4 hours, however, a longer term half-life of about 15 hours has been reported in studies where blood has been sampled up to 48 hours.

The single-dose pharmacokinetics of KADIAN® are linear over the dosage range of 30 to 100 mg. The single dose and multiple dose pharmacokinetic parameters of KADIAN® in normal volunteers are summarized in Table 1.

Table 1: Mean pharmacokinetic parameters (% coefficient variation) resulting from a fasting single dose study in normal volunteers and a multiple dose study in patients with cancer pain.

Regimen/ Dosage Form	AUC[a,c] (ng.h/mL)	C_{max}[b] (ng/mL)	T_{max} (h)	C_{min}[c] (ng/mL)	Fluctuation[c]
Single Dose (n=24)					
KADIAN® Capsule	271.0 (19.4)	15.6 (24.4)	8.8 (41.1)	na[d]	na
Extended-Release Tablet	304.3 (19.1)	30.5 (32.1)	2.5 (52.6)	na	na
Morphine Solution	362.4 (42.6)	64.4 (38.2)	0.9 (55.6)	na	na
Multiple Dose (n=24)					
KADIAN® Capsule q24h	560.9 (38.6)	17.3 (37.7)	10.3 (32.2)	3.9 (52.3)	3.0 (45.5)
Extended-Release Tablet q12h	457.3 (40.2)	36.9 (42.0)	4.4 (53.0)	7.6 (60.3)	4.1 (51.5)

[a] For single dose AUC = AUC_{0-48h}, for multiple dose AUC = AUC_{0-24h} at steady state.
[b] For single dose parameter normalized to 100 mg, for multiple dose parameter normalized to 100 mg per 24 hours.
[c] Steady-state fluctuation in plasma concentrations = $(C_{max}-C_{min})/C_{min}$.
[d] Not applicable

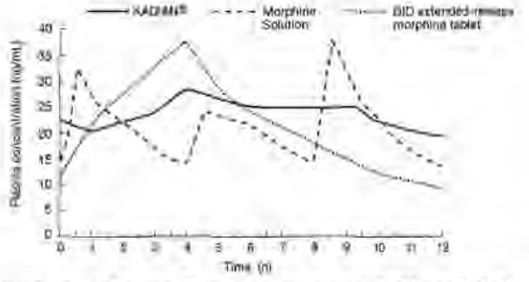
Absorption

Following the administration of oral morphine solution, approximately 50% of the morphine absorbed reaches the systemic circulation within 30 minutes. However, following the administration of an equal amount of KADIAN® to healthy volunteers, this occurs, on average, after 8 hours. As with most forms of oral morphine, because of pre-systemic elimination, only about 20 to 40% of the administered dose reaches the systemic circulation.

Food Effects: While concurrent administration of food slows the rate of absorption of KADIAN®, the extent of absorption is not affected and KADIAN® can be administered without regard to meals.

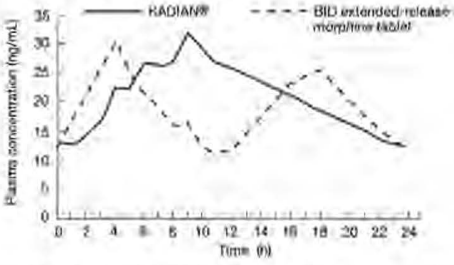
Steady State: When KADIAN® is given on a fixed dosing regimen to patients with chronic pain due to malignancy, steady state is achieved in about two days. At steady state, KADIAN® will have a significantly lower C_{max} and a higher C_{min} than equivalent doses of oral morphine solution and some other extended-release preparations (see Graph 1).

Graph 1 (Study # MOR 1/90): Mean steady state plasma morphine concentrations for KADIAN® (twice a day), extended-release morphine tablet (twice a day) and oral morphine solution (every 4 hours); plasma concentrations are normalized to 100 mg every 24 hours. (n=24)



When given once daily (every 24 hours) to 24 patients with malignancy, KADIAN® had a similar C_{max} and higher C_{min} at steady state in clinical usage, when compared to twice-daily (every 12 hours) extended-release morphine tablets, given at an equivalent total daily dosage (see Graph 2 and Table 1). Drug-disease interactions are frequently seen in the older and more gravely ill patients, and may result in both altered absorption and reduced clearance as compared to normal volunteers (see **Geriatric, Hepatic Failure,** and **Renal Insufficiency** sections).

Graph 2 (Study # MOR 9/92): Dose normalized mean steady state plasma morphine concentrations for KADIAN® (once a day), and an equivalent dose of a 12-hour, extended-release morphine tablet given twice a day. Plasma concentrations are normalized to 100 mg every 24 hours. (n=24).



Distribution

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. The volume of distribution of morphine is approximately 3 to 4 L/kg. Morphine is 30 to 35% reversibly bound to plasma proteins. Although the primary site of action of morphine is in the CNS, only small quantities pass the blood-brain barrier. Morphine also crosses the placental membranes [see **PRECAUTIONS - Pregnancy**] and has been found in breast milk (see **PRECAUTIONS - Nursing Mothers**).

Metabolism

The major pathway of the detoxification of morphine is conjugation, either with D-glucuronic acid or the liver to produce glucuronides or with sulfuric acid to give morphine-3-ethereal sulfate. 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, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5 to 15%). Studies in healthy subjects and cancer patients have shown that the glucuronide metabolite to morphine mean molar ratios (based on AUC) are similar after both single doses and at steady state for KADIAN®, 12-hour extended-release morphine sulfate tablets and morphine sulfate solution.

M3G has no significant analgesic activity. M6G has been shown to have opioid agonist and analgesic activity in humans.

Excretion

Approximately 10% of morphine dose is excreted unchanged in the urine. Most of the dose is excreted in the urine as M3G and M6G. A small amount of the glucuronide metabolites is excreted in the bile and there is some minor enterohepatic cycling. Seven to 10% of administered morphine is excreted in the feces.

The Journal of Pain, Vol 9, No 4 (April), 2008: pp 330-336
Available online at www.sciencedirect.com

ELSEVIER

Effect of Concomitant Ingestion of Alcohol on the In Vivo Pharmacokinetics of KADIAN (Morphine Sulfate Extended-Release) Capsules

Franklin Johnson, George Wagner, Stephen Sun, and Joseph Stauffer
Alpharma Pharmaceuticals LLC, Piscataway, New Jersey.

Abstract: **The recent withdrawal of hydromorphone hydrochloride extended-release capsules (Palladone; Purdue Pharma L.P., Stamford, CT) from the market after pharmacokinetic data revealed a risk of alcohol-induced dose-dumping prompted a re-examination of the risk-benefit profiles of extended-release drugs. Although warnings on concomitant alcohol use are included on opioid product labels, further investigations of extended-release formulations to determine the risk of dose-dumping were recommended by the US Food and Drug Administration. The present study was undertaken to assess the single-dose relative bioavailability of polymer-coated, extended-release morphine sulfate capsules (KADIAN, 100 mg; Alpharma Pharmaceuticals LLC, Piscataway, NJ). This open-label, randomized, 3-way crossover study with an additional index arm, conducted among 32 healthy male volunteers, found no significant evidence of a formulation interaction between KADIAN and alcohol, in vivo. The pharmacokinetics of serum morphine did not differ significantly among subjects taking KADIAN with water (fasted) or with 240 mL 40% alcohol under fasted or fed conditions. Analysis of variance ratios of least-squares means for ln-transformed AUC_{∞} and C_{max} satisfied the criteria (90% confidence intervals within 80%–125%) to declare no drug formulation interaction among the KADIAN regimens dosed with alcohol compared with KADIAN taken with water. There were no serious adverse events or deaths reported during the study.**

Perspective: ***Because of the high rate of alcohol use in the United States, the potential for drug-alcohol interactions is an important clinical concern. Although it is recommended that alcohol not be used while the patient is taking opioids, results of this in vivo study indicate that the risk of alcohol-induced dose-dumping in connection with the use of KADIAN is negligible.***

Key words: *KADIAN, opioid, morphine sulfate extended-release, alcohol, naltrexone, pharmacokinetics.*

Alcohol enhances the effects of opioids on the central nervous system (CNS), and even moderate drinking may pose a risk of potential drug-drug interaction.[20] Results of the 2005 National Survey on Drug Use and Health indicate a high rate of alcohol use among Americans. Sixty-seven percent of those aged 21 to 25 years, and nearly half of those aged 60 to 64 years, had consumed alcohol in the previous month.[13] The Drug Abuse Warning Network (DAWN) reported that concomitant use of alcohol and pharmaceuticals, with or without other illicit drugs, accounted for 13.5% of total drug-related emergency room visits in 2005.[12] The possibility of concomitant use of alcohol with pain medication, including opioids, is a reasonable concern. The dangers of concomitant consumption of alcohol and extended-release opioids have recently attracted attention in the scientific and regulatory arenas.

Extended-release formulations contain enough opioid to provide analgesia over the dosing interval, generally 12 to 24 hours. There are several strategies used in creating extended-release tablets and capsules. Tablet formulations contain opioid enmeshed within a matrix consisting of polymers that are hydrophobic, hydrophilic, or combinations of more than 1 type of polymer.[7-11] On tablet ingestion, the hydrophilic polymer swells in the gastrointestinal (GI) fluid. Drug release can be controlled by the

Received June 6, 2007; Revised November 1, 2007; Accepted November 9, 2007.
Supported by Alpharma Pharmaceuticals LLC, Piscataway, New Jersey.
Address reprint requests to Franklin Johnson, Clinical Pharmacology, Alpharma Pharmaceuticals LLC, 1 New England Avenue, Piscataway, NJ 08854. E-mail: franklin.johnson@alpharma.com
1526-5900/$34.00

doi:10.1016/j.jpain.2007.11.009

rates of diffusion of liquid into the tablet and diffusion of drug into the system, or by the partition coefficients of the drug between the 2 polymer types.[7,9,11] Some tablet formulations may use 2 types of hydrophobic polymer matrices, which enable dual control: One component can be released immediately upon contact with GI fluids, and a sustained-release component can be released by slower diffusion through the matrix pores.[10,11]

Capsule formulations adsorb morphine onto an inert core bead, which is then enclosed within a polymer coating. The chemistry of the polymer (hydrophobicity, pH dependence) surrounding each bead controls the rate of release of active drug.[1,3,4,19] One formulation uses fumaric acid as an osmotic agent and local pH modifier. Inclusion of beads that are not enclosed within a rate-limiting polymer produces immediate-release beads.[2]

After a pharmacokinetic (PK) study in healthy volunteers indicated a potentially fatal interaction between alcohol and hydromorphone hydrochloride extended-release capsules (Palladone; Purdue Pharma L.P., Stamford, CT), the US Food and Drug Administration (FDA) requested the removal of this opioid from the market. In the study, co-ingestion of Palladone with 240 mL (8 oz) of 40% (80 proof) alcohol raised peak plasma hydromorphone concentrations approximately 6-fold, compared with ingestion with water. One subject in this study experienced a 16-fold increase in peak plasma hydromorphone concentrations after ingesting Palladone with 40% alcohol compared with water.[19] Of interest, the in vivo PK study showed that lower concentrations of alcohol, eg, a mixed drink (20% alcohol) or beer (4% alcohol), also led to potentially serious increases in hydromorphone concentrations.[14]

After the withdrawal of Palladone from the market, the FDA recommended that makers of other extended-release formulations conduct investigations to determine the risk of alcohol-induced dose-dumping, whereby alcohol interacts with the extended-release characteristics to yield unintended, rapid drug release in a short period of time.[6,14] In vitro studies conducted with an extended-release formulation of morphine sulfate (AVINZA; King Pharmaceuticals, Inc., Bristol, TN) demonstrated accelerated release of morphine in buffer solutions containing ethanol. As a result, the AVINZA label was revised to warn against consumption of alcohol and use of medications containing alcohol while taking the product.[2,5] Similar information was placed as a Black Box Warning for extended-release oxymorphone hydrochloride (OPANA ER; Endo Pharmaceuticals, Chadds Ford, PA) due to results of an in vivo study examining the effect of alcohol on the bioavailability of a single 40-mg dose in healthy fasted volunteers.[8]

The current study was conducted to assess the single-dose bioavailability of morphine sulfate extended-release capsules (KADIAN; Alpharma Pharmaceuticals LLC, Piscataway, NJ) when dosed with alcohol in the fasted and fed conditions relative to KADIAN administered with water.

Materials and Methods

Objective

The objective of this study was to compare the single-dose relative bioavailability of KADIAN (100 mg) when dosed with alcohol under fasted and fed conditions versus water.

Participants

Participants were opioid-naive, healthy, adult male volunteers (N = 32) with a mean age of 24 years (range, 21–37 years). To be eligible for participation, subjects were required to have a history of moderate alcohol consumption, operationally defined as at least 7 to 21 units of alcohol per week, with 1 alcohol unit equivalent to 12 oz of beer or 1.5 oz of 80-proof (40% alcohol) distilled spirits. The inclusion criteria also specified that subjects were nonsmokers for at least 3 months or light smokers (<10 pack-years), were within 20% of their ideal weight, and had no clinically significant laboratory abnormalities during screening. Exclusion criteria included history of alcoholism or drug abuse; history of no alcohol intake; less than moderate, or excessive alcohol intake; history or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, GI, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease; hypersensitivity to morphine, other opioids, or opioid antagonists; and other physical or laboratory abnormalities considered clinically significant. The protocol for this study was approved by the MDS Pharma Services institutional review board, and informed consent was obtained from each participant.

Study Design

This was an open-label, single-dose, 3-way crossover PK drug interaction study between 100 mg KADIAN and 40% alcohol in the fasted and fed conditions and 100 mg KADIAN with water administered in a randomized fashion. Pharmacokinetics of an immediate-release morphine oral solution (20 mg) without alcohol in the fasted condition, as an index arm, were explored during the fourth period.

Typically, subjects enrolled in PK studies are healthy, opioid-naive, adult volunteers. As such, it is common practice to provide 1 or more oral administrations of the opioid receptor antagonist, naltrexone hydrochloride, before dosing with an opioid to attenuate opioid-induced adverse events (AEs), in particular, vomiting and respiratory depression. Therefore, in this study, naltrexone hydrochloride (50 mg tablet) was administered with 240 mL of water at 12 hours and 2 hours before treatment.

Regimens

Subjects were randomly assigned to begin with 1 of the following regimens:

- Regimen A: KADIAN 100 mg + 240 mL 40% alcohol (four 60-mL shots of 40% [80-proof] alcohol [101 mL

190-proof Everclear (Luxco, St. Louis, MO), 139 mL water]) under fasted conditions
- Regimen B: KADIAN 100 mg + 240 mL 40% alcohol (four 60-mL shots of 40% [80-proof] alcohol) immediately after ingestion of a standard FDA high-fat meal
- Regimen C: KADIAN 100 mg + 240 mL water under fasted conditions

Subjects were required to consume all alcohol (or water) within 20 minutes of dosing.

All subjects who completed the study then received the following regimen during period 4:
- Regimen D: Concentrated oral morphine solution (20 mg/5 mL) 5 mL + 235 mL water under fasted conditions

Procedures

Subjects assigned to regimens A, B, or C were housed at the study center from at least 15 hours before dosing until 36 hours after dosing. They returned for a 48-hour blood sample. Subjects assigned to regimen D were housed until completion of the 24-hour blood sample. At check-in, each subject was screened for alcohol and various controlled substances. In addition, serum aspartate transaminase, serum alanine transaminase, and serum amylase assessments were repeated at each check-in, whereas hemoglobin and hematocrit were assessed at check-in for subjects in regimens C and D.

All subjects were fed according to a standardized meal schedule. For those undergoing the fasted regimens (A, C, and D), food was restricted from 10 hours before dosing until 4 hours after dosing. Subjects assigned to regimen B consumed a standard high-fat breakfast within 30 minutes before dosing. A 7-day washout period separated each regimen.

Pharmacokinetic blood sampling (ie, serum morphine and metabolites) took place before dosing and at the following time intervals after dosing for regimens A, B, and C: 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 7.0, 8.0, 9.0, 10, 12, 18, 24, 36, and 48 hours. For regimen D, blood samples were collected before dosing and at 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, and 24 hours after dosing. An overview of the study design is presented in Fig 1.

Pharmacokinetic Analyses

Pharmacokinetic measurements for serum morphine, morphine-3-glucuronide, and morphine-6-glucuronide included the following parameters: AUC_{0-t}, the area under the serum concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method; AUC_{∞}, the area under the serum concentration versus time curve from time 0 to infinity, calculated as the sum of AUC_{0-t} plus the ratio of the last measurable serum concentration to the elimination rate constant; percentage of AUC extrapolated; C_{max}, the maximum measured serum concentration over the time span specified; T_{max}, the time of the maximum measured serum concentration; k_{el}, the apparent first-order terminal elimination rate constant calculated from a semilogarithmic plot of the serum concentration versus time curve; and $t_{½}$, the apparent first-order terminal elimination half-life calculated as $0.693/k_{el}$.

Statistical Analyses

Analyses of variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, AUC_{∞}, and C_{max} PK parameters for regimens A, B, and C. Each ANOVA included calculation of ratios of least-squares means (LSMs), the differences between regimen LSMs, and the standard error associated with these differences. LSMs ratios were expressed as a percentage relative to the reference regimen (C). The comparisons of interest were A versus C and B versus C. In addition, A versus D (the oral morphine solution) was compared for investigational purposes. Ninety percent confidence intervals (CIs) for the ratios of the LSMs of regimens A and B, relative to regimen C, were calculated from the ln-transformed AUC_{∞} and C_{max} data. Calculation of these 90% CIs was consistent with the statistical test for bioequivalence. Traditional criteria for bioequivalence recommend that ratios for AUC_{∞} and C_{max} fall within the limits of 80% to 125%.[16-18]

Safety Assessments

Safety and tolerability were assessed by monitoring AEs, clinical laboratory results, vital signs, ECGs, and physical examinations. In addition, alcohol blood tests and alcohol breath tests were performed.

Results

The study population consisted of 32 adult male volunteers, with a mean age of 24 years (range, 21–37 years), mean height of 182 cm (range, 168–193 cm),

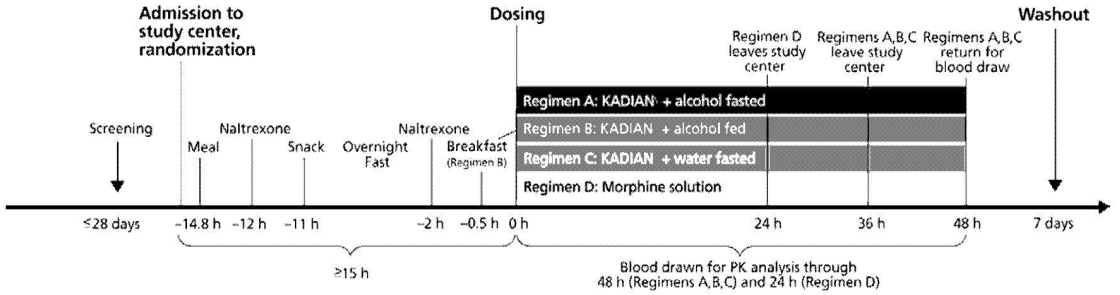


Figure 1. Study design.

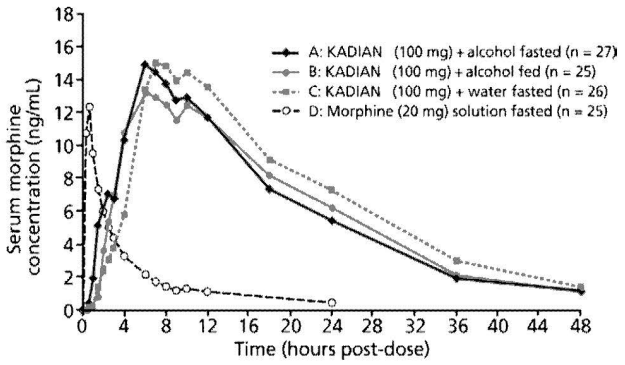


Figure 2. Mean serum morphine concentration-time profiles for all subjects with evaluable data.

and mean weight of 81.0 kg (range, 70.8–99.8 kg). Of the 32 subjects enrolled in the study, PK analyses were performed on data from 27 subjects, as 5 subjects did not complete at least 2 study periods enabling a comparison either of regimens A versus C or B versus C. One subject was included in the PK analysis but excluded from the ANOVA because of a protocol deviation (regimen C was not administered). Seven subjects discontinued the study, 5 due to AEs (3 due to vomiting, 1 due to chest pain, and 1 due to streptococcal pharyngitis), 1 due to a positive urine drug screen for amphetamines, and 1 who withdrew from the study before starting regimen D.

Pharmacokinetic Results

Mean serum morphine concentration-time profiles for all subjects with evaluable data are illustrated in Fig 2. The serum morphine profile after coadministration of regimens A (KADIAN + 40% alcohol fasted) or B (KADIAN + 40% alcohol fed) was comparable to the serum morphine profile after regimen C (KADIAN + water). Peak absorption was reached at a median T_{max} of 8 hours after dosing for all 3 regimens. The serum profile of regimen D (oral morphine solution, 20 mg) is also displayed in Fig 2 for visual comparison with the extended-release morphine time-release profiles.

The FDA Guidance for Industry regarding bioavailability and bioequivalence studies for orally administered drugs recommends that data from subjects taking modified-release products who experience vomiting at any time during the dosing interval (12 hours for KADIAN) can be excluded from statistical analyses.[17]

Eleven subjects who were included in the overall analysis vomited at times ranging from 0.17 to 11.85 hours after administration of regimen A. Five of them also vomited after administration of regimen B, at times ranging from 0.08 to 7.85 hours. No subject vomited after taking regimen C, with the exception of 1 subject who vomited but also had strep throat and was withdrawn from the study. The mean serum morphine concentration-time profile for the group of subjects excluding those who had vomited within 12 hours of dosing was similar to the group that included all subjects. Fig 3 displays the mean serum morphine concentration-time profiles for these subjects.

Both profiles demonstrate that the extended-release characteristics of KADIAN were maintained in the presence of alcohol. A summary of the PK parameters for all subjects with evaluable data, as well as the group excluding patients who had vomited within 12 hours, is presented in Table 1.

Overall mean exposure (AUC) was similar between the KADIAN regimens (A, B, and C), and to regimen D when dose-normalized to 100 mg. Mean C_{max} for regimens A, B, and C were similar and were approximately one-fourth of the dose-normalized C_{max} for regimen D. Median T_{max} was 8.0 hours (range, 2.5 to 18 hours) for all 3 KADIAN regimens. The mean $t_{½}$ for KADIAN was approximately 11 hours.

The ANOVA ratios of LSMs for AUC and C_{max} are presented in Table 2. This table includes all subjects who had PK data for a comparison of interest, either regimens A/C and/or regimens B/C (n = 26 for all subjects; n = 21 for all subjects excluding those who vomited within the 12-hour dosing interval). Comparisons of regimens A/C and B/C 90% CIs for the ratio of geometric means for AUC_{∞} and C_{max} were within the 80% to 125% acceptance range for CI boundaries to declare no drug formulation interaction.

In addition, individual subject C_{max} ratios of regimens A/C versus B/C were calculated. The ratios were similar for most subjects. This trend is depicted in Fig 4. C_{max} ratios ranged from 0.43 to 1.89 (overall median, 1.00), with the exception of 1 subject whose C_{max} ratio was 4.54 for regimen A versus C. For this subject, the serum morphine concentration-time profile after regimen A still showed a time-release pattern consistent with an extended-release formulation. The T_{max} was 6 hours, and C_{max} was approximately 42% lower than the dose-normalized mean C_{max} for regimen D (oral morphine solution), which suggests the extended-release mechanism of KADIAN was not affected. The data also include 1 subject who did not consume the fourth shot of alcohol in regimen A due to an AE (vomiting), but whose PK values fell within the range for those of the other subjects.

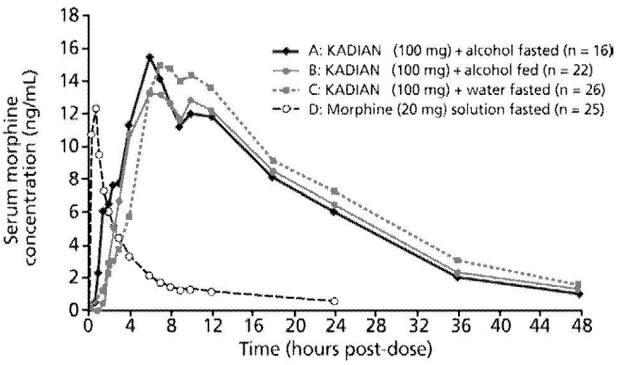


Figure 3. Mean serum morphine concentration-time profiles excluding subjects with emesis within the 12-hour dosing interval.

Table 1. Summary of Serum Morphine Pharmacokinetic Parameters

Parameter	Regimen A KADIAN + Alcohol Fasted	Regimen B KADIAN + Alcohol Fed	Regimen C KADIAN + Water Fasted	Regimen D Dose-Normalized OS + Water Fasted
All subjects with evaluable pharmacokinetic data				
AUC_{0-t}[a] (ng · h/mL)	271.80 (35.5) (n = 27)	279.33 (29.3) (n = 25)	307.2 (32.2) (n = 26)	231.8 (31.6) (n = 25)
AUC_{∞}[a]* (ng · h/mL)	300.68 (39.2) (n = 26)	301.6 (33.7) (n = 25)	337.28 (33.3) (n = 26)	347.8 (27.2) (n = 18)
C_{max}[a] (ng/mL)	16.95 (42.1) (n = 27)	15.71 (30.3) (n = 25)	16.46 (32.9) (n = 26)	68.4 (39.0) (n = 25)
T_{max}[b] (h)	8.0 (4–24) (n = 27)	8.0 (2.5–18) (n = 25)	8.0 (6–18) (n = 26)	0.67 (0.33–1.5) (n = 25)
$t_{1/2}$[c]* (h)	11.8 (4.89) (n = 26)	10.8 (3.20) (n = 25)	11.6 (4.46) (n = 26)	14.3 (8.40) (n = 18)
Excluding subjects with emesis within 12-hour dosing interval				
AUC_{0-t}[a] (ng · h/mL)	283.22 (32.2) (n = 16)	290.37 (21.2) (n = 22)	307.2 (32.2) (n = 26)	231.8 (31.6) (n = 25)
AUC_{∞}[a]* (ng · h/mL)	305.74 (32.3) (n = 15)	311.36 (23.0) (n = 22)	337.28 (33.3) (n = 26)	347.8 (27.2) (n = 18)
C_{max}[a] (ng/mL)	16.96 (35.4) (n = 16)	16.03 (29.1) (n = 22)	16.46 (32.9) (n = 26)	68.4 (39.0) (n = 25)
T_{max}[b] (h)	6.0 (4–24) (n = 16)	8.0 (4–18) (n = 22)	8.0 (6–18) (n = 26)	0.67 (0.33–1.5) (n = 25)
$t_{1/2}$[c]* (h)	9.96 (3.11) (n = 15)	10.5 (2.56) (n = 22)	11.6 (4.46) (n = 26)	14.3 (8.40) (n = 18)

OS = oral morphine solution.

[a]Geometric mean (CV%); [b]Median (range); [c]Arithmetic mean (SD).

*Extrapolated parameters AUC_{∞} and $t_{1/2}$ could not be estimated for some subjects.

The morphine-3-glucuronides and morphine-6-glucuronides were also measured during the study. Mean serum morphine-3- and morphine-6-glucuronide concentration-time profiles are presented in Figs 5 and 6, respectively. Visual inspection of the mean profiles shows that although the mean peak concentrations with concomitant alcohol administration were slightly greater than the reference treatment, concentrations at the end of terminal elimination phase were similar to the reference treatment. The mean profiles suggest that concomitant alcohol administration did not adversely affect morphine metabolism, nor was there any evidence in the terminal phase to suggest the likelihood of metabolite accumulation from multiple dosing with KADIAN and alcohol. Furthermore, ANOVA results for the ln-transformed mean AUC ratios of LSMs provided CIs within 80% to 125% for both metabolites, confirming that the total exposures of both metabolites were not significantly affected by alcohol coadministration.

Table 2. ANOVA Ratios of Least-Squares Means

	Regimen	Ratio of LSMs, %	90% CI (lower; upper)
Subjects with at least 1 comparison of interest (n = 26)			
AUC_{∞}(ng · h/mL)	A/C	89.1	80.3; 98.9
	B/C	89.7	80.7; 99.6
C_{max} (ng/mL)	A/C	102.3	89.5; 116.8
	B/C	98.0	85.5; 112.3
Subjects with at least 1 comparison of interest excluding those with emesis within 12-hour dosing period (n = 21)			
AUC_{∞}(ng · h/mL)	A/C	96.3	89.4; 103.8
	B/C	94.6	88.7; 100.9
C_{max} (ng/mL)	A/C	107.6	93.5; 123.8
	B/C	100.9	89.1; 114.3

Safety Results

There were no reported incidents of respiratory depression during the study, nor were there any serious AEs or deaths. Overall, 27 subjects (84%) experienced at least 1 AE that was possibly or probably related to the administration of multiple drugs: 21 subjects (66%) with regimen A (KADIAN 100 mg + alcohol [fasted]), 19 subjects (59%) with regimen B (KADIAN 100 mg + alcohol [fed]), 7 subjects (22%) with regimen C (KADIAN 100 mg + water [fasted]), and 3 subjects (9%) with regimen D (morphine sulfate 20 mg oral solution [fasted]). Most AEs were mild to moderate, the most frequent being nausea (15 subjects), vomiting (15 subjects), headache (14 subjects), and som-

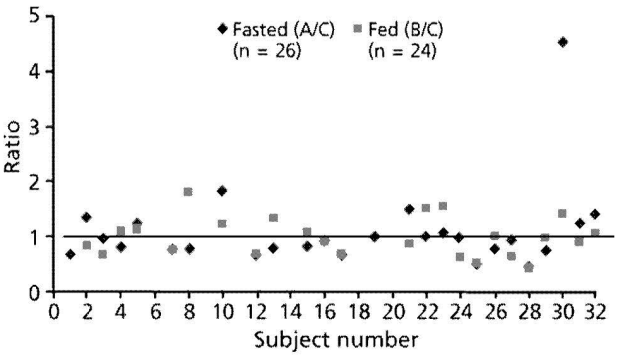
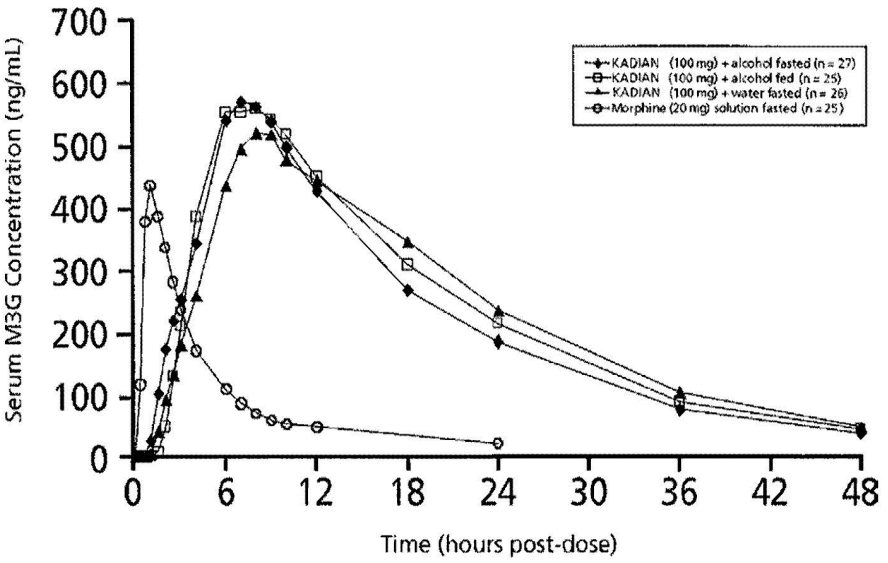


Figure 4. C_{max} ratio of KADIAN + alcohol versus KADIAN + water for each subject.



Abbreviation: M3G, morphine-3-glucuronide.

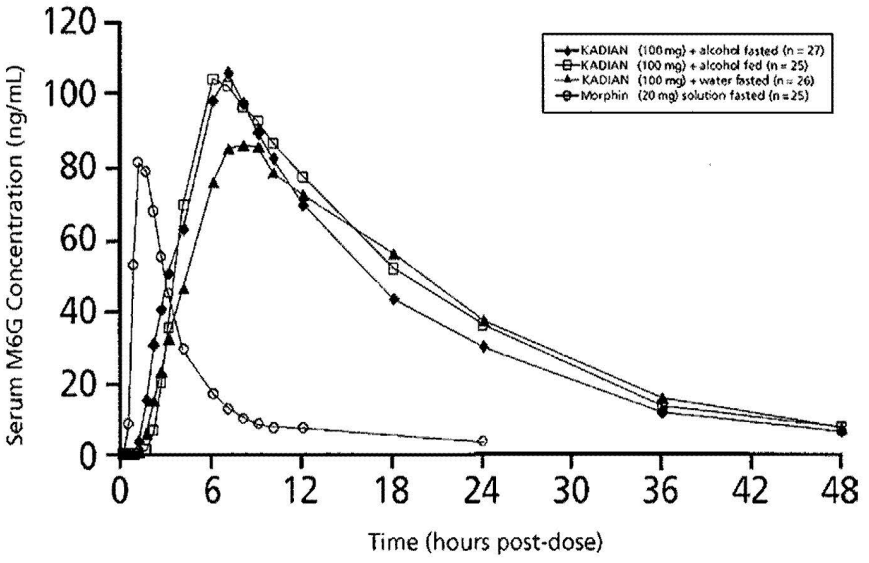
Figure 5. Mean M3G concentration-time profile for all subjects.

nolence (or "feels intoxicated," 12 subjects). The 1 severe AE, chest pain, was deemed unlikely to be related to the study regimen. All AEs resolved before the end of the study. There were no important changes in clinical laboratory results, vital signs, ECGs, and physical examinations. Serum ethanol concentrations were determined to 10 hours post-dose after regimens A and B for safety analysis. The rate and extent of absorption of ethanol was attenuated in the presence of food.

Discussion

No drug interaction between alcohol and KADIAN was observed in this study. Furthermore, since the in vivo data suggest that rate and extent of absorption of morphine from KADIAN dosed with alcohol under fasted or fed conditions was similar to that of KADIAN given with water under fasted conditions, the extended-release mechanism of the KADIAN formulation was not significantly affected by 40% alcohol. The FDA has reviewed data from this study, has concurred that there is no interaction between KADIAN and alcohol in vivo when administered concomitantly, and has not required any changes to the package insert.[15]

It is not yet known why some extended-release opioid formulations are subject to dose-dumping in alcohol and others are not. Potential reasons may relate to the characteristics of the opioid or to the extended-release mechanisms themselves.



Abbreviation: M6G, morphine-6-glucuronide.

Figure 6. Mean M6G concentration-time profile for all subjects.

The KADIAN shell is composed of a combination of pH-independent and pH-dependent water-soluble polymers interspersed within a water-insoluble polymer matrix. This unique combination results in pH-dependent drug release from KADIAN. Although the exact mechanism is not well understood, the poor solubility of the pH-dependent polymer, methacrylic acid copolymer, at low pH, may offer sufficient protection from coingested alcohol while the capsule is in the stomach, where alcohol would be quickly absorbed. The copolymer then gradually dissolves with increasing pH as the capsule moves from the stomach through the GI tract to release the morphine sulfate.

While KADIAN maintained its extended-release profile after co-ingestion with alcohol, consumption of alcohol with any morphine product, whether immediate- or extended-release, is not recommended. All opioids, including KADIAN, may be expected to have additive effects and potentially serious outcomes when used in conjunction with alcohol, other opioids, or illicit drugs that cause CNS depression.[4]

In calling for careful evaluation of the potential for dose-dumping with extended-release dosage forms, the FDA acknowledged that product labeling and other means of informing patients about potential drug-alcohol interactions may not always be effective. The development of extended-release formulations that are not sensitive to alcohol is a goal.[6] Further investigations of social drinking and prolonged moderate alcohol intake may clarify the potential for drug interactions when extended-release formulations are ingested with alcohol.

Acknowledgments

Technical expertise was provided by Alfred Liang, Alpharma Pharmaceuticals LLC. Writing and editorial support for this manuscript was provided by Innovex Medical Communications, Parsippany, NJ.

References

1. American Pharmacists Association. Palladone Capsules New Product Bulletin. 2004. Washington, DC, American Pharmacists Association

2. AVINZA [package insert]. 2006. Bristol, TN, King Pharmaceuticals, Inc

3. Gourlay GK: Sustained relief of chronic pain: Pharmacokinetics of sustained release morphine. Clin Pharmacokinet 35:173-190, 1998

4. KADIAN [package insert]. 2007, Piscataway, NJ, Alpharma Pharmaceuticals LLC

5. Ligand Pharmaceuticals Inc. Dear Health Care Professional Letter. 2005. Ligand Pharmaceuticals Inc

6. Meyer RJ, Hussain AS: Awareness Topic: Mitigating the Risks of Ethanol Induced Dose Dumping from Oral Sustained/Controlled Release Dosage Forms. 2005. FDA Advisory Committee for Pharmaceutical Services Meeting

7. MS Contin [package insert]. 2005. Stamford, CT, Purdue Pharma LP

8. OPANA ER [package insert]. 2007. Chadds Ford, PA, Endo Pharmaceuticals Inc

9. Oramorph SR [package insert]. 2005. Wilmington, NC, aaiPharma Inc

10. Oxycodone hydrochloride extended-release tablets [package insert]. 2004. Chadds Ford, PA, Endo Pharmaceuticals Inc

11. Reder RF: Opioid formulations: Tailoring to the needs in chronic pain. Eur J Pain 5(Suppl A):109-111, 2001

12. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Drug Abuse Warning Network, 2005: National Estimates of Drug-Related Emergency Department Visits. 2007. Rockville, MD. DAWN Series D-29, DHHS Publication No. (SMA) 07-4256

13. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration Office of Applied Studies. National Survey on Drug Use and Health (NSDUH). 2005, US Department of Health and Human Services. Substance Abuse and Mental Health Services Administration Office of Applied Studies

14. US Food and Drug Administration. Palladone (Hydromorphone Hydrochloride Extended-Release) Capsules: Questions and Answers. 2005. US Food and Drug Administration

15. US Food and Drug Administration. Letter to Alpharma Pharmaceuticals NDA 20-616/S-017 and S-021. 2-27-2007. Rockville, MD, US Food and Drug Administration

16. US Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry: In Vivo Drug Metabolism/Drug Interaction Studies-Study Design, Data Analysis, and Recommendations for Dosing and Labeling. 1999. US Food and Drug Administration, Center for Biologics Evaluation and Research

17. US Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products–General Considerations. 2007. US Food and Drug Administration, Center for Drug Evaluation and Research

18. US Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. 2002, US Food and Drug Administration, Center for Drug Evaluation and Research

19. US Food and Drug Administration. FDA Alert: Alcohol-Palladone Interaction. Alert for Healthcare Professionals: Hydromorphone hydrochloride extended-release capsules. 7-13-2005. US Food and Drug Administration. 2-23-2007

20. Weathermon R, Crabb DW: Alcohol and medication interactions. Alcohol Res Health 23:40-54, 1999