Kadian / NDA

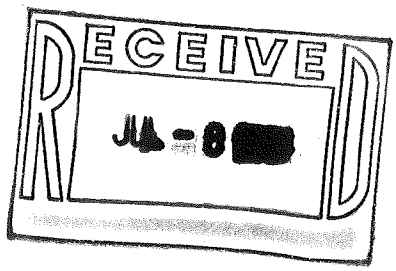
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-616

JUL 3 1996



Faulding Services Incorporated
200 Elmora Ave.
Elizabeth, New Jersey 07207

Attention: George Wagner
Manager, Regulatory Affairs

Dear Mr. Wagner:

Please refer to your June 29, 1995 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kadian (morphine sulfate) Sustained Release Capsules, 20 mg, 50 mg and 100 mg.

We acknowledge receipt of your amendments dated October 11, 1995; April 22 and 25; June 11, 12 and 17; and July 1, 1996.

This new drug application provides for a sustained release formulation of morphine sulfate for the management of moderate to severe pain where treatment with an opioid analgesic is indicated for more than a few days.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-616. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Bonnie McNeal, M.A.
Project Manager
(301) 443-3741

Sincerely yours,

Curtis Wright, M.D., M.P.H.
Acting Director
Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE
Draft Labeling

LABELING

JUL 3 1996

KADIAN™
Morphine Sulfate Sustained-release

CII

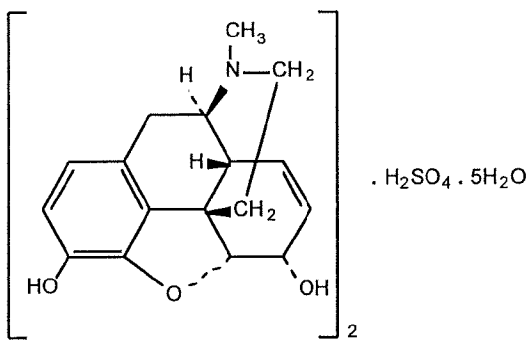
KADIAN™ 20 mg Capsules
KADIAN™ 50 mg Capsules
KADIAN™ 100 mg Capsules

Warning: May be habit forming

DESCRIPTION

KADIAN™ capsules 20, 50 and 100 mg contain identical polymer coated sustained-release pellets of morphine sulfate 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_b is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4).

Each KADIAN™ Sustained-release Capsule contains either 20, 50 or 100 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: Hydroxypropyl Methylcellulose, Ethylcellulose, Methacrylic Acid Copolymer, Polyethylene Glycol, Diethyl Phthalate, Talc, Black Ink SW-9009, Corn Starch and Sucrose.

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 therapeutic actions of morphine are analgesia, sedation and alterations of mood. Opioids of this class do not usually eliminate pain, but they do reduce the perception of pain by the central nervous system.

Morphine produces respiratory depression by reducing the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension (or to direct electrical stimulation).

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

Morphine causes miosis, even in total darkness, and little tolerance develops to this effect. Pinpoint pupils are a sign of 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 due to severe hypoxia in overdose situations.

Effects on the Gastrointestinal Tract

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of 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
The relationship between the blood level of morphine and the analgesic response will depend on the patient's age, state of health, medical condition, and the extent of previous opioid treatment.

A minimum effective concentration (MEC) of morphine for pain relief has been reported as 27.2 ± 14.5 ng/mL (mean ± SD) in cancer patients treated with morphine solution. These results compare with the MEC for plasma morphine reported as 14.7 ± 4.8 ng/mL (mean ± SD) in patients with postoperative pain. The high degree of variation is of clinical significance as it may result in either under-dosing or over-dosing if the dosage is not adjusted to the patient's clinical status and analgesic response (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

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

Pharmacokinetics
KADIAN™ capsules contain polymer coated sustained-release pellets of morphine sulfate that release morphine significantly more slowly than from morphine sulfate tablets and shorter-acting controlled-release oral morphine sulfate preparations. KADIAN™ activity is primarily due to morphine. One metabolite, morphine-6-glucuronide, has been shown to have analgesic activity, but poorly crosses the blood-brain barrier.

Following oral administration, the extent of absorption is essentially the same for immediate or sustained-release formulations, although the time to peak blood level (T_{max}) will be longer and the C_{max} will be lower for formulations that delay the release of morphine 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#,+ (ng.h/mL)	Cmax+ (ng/mL)	Tmax (h)	Cmin+ (ng/mL)	Fluctuation*
Single Dose (n=24)					
KADIAN™ Capsule	271.0 (19.4)	15.6 (24.4)	8.6 (41.1)	na^	na
Controlled-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 (55.8)	na	na
Multiple Dose (n=24)					
KADIAN™ Capsule q24h	500.9 (38.6)	37.3 (37.7)	10.3 (32.2)	9.9 (52.3)	3.0 (45.5)
Controlled-Release Tablet q12h	457.3 (40.2)	36.9 (42.0)	4.4 (53.0)	7.6 (60.3)	4.1 (51.5)

For single dose AUC = AUC_{0-48h}, for multiple dose AUC = AUC_{0-24h} at steady state
+ For single dose parameter normalized to 100 mg, for multiple dose parameter normalized to 100 mg per 24 hours
* Steady-state fluctuation in plasma concentrations = Cmax-Cmin/Cmin
^ Not applicable

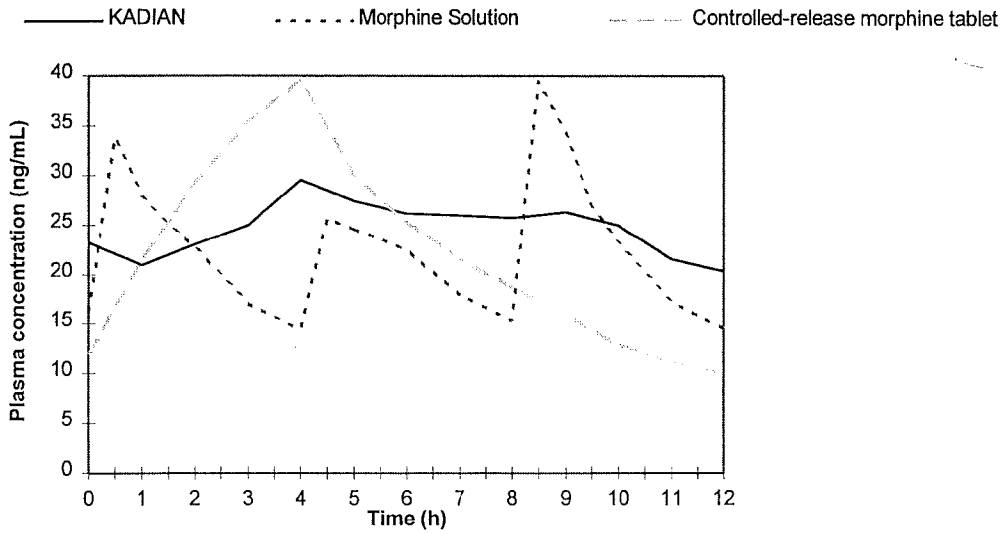
Absorption

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.

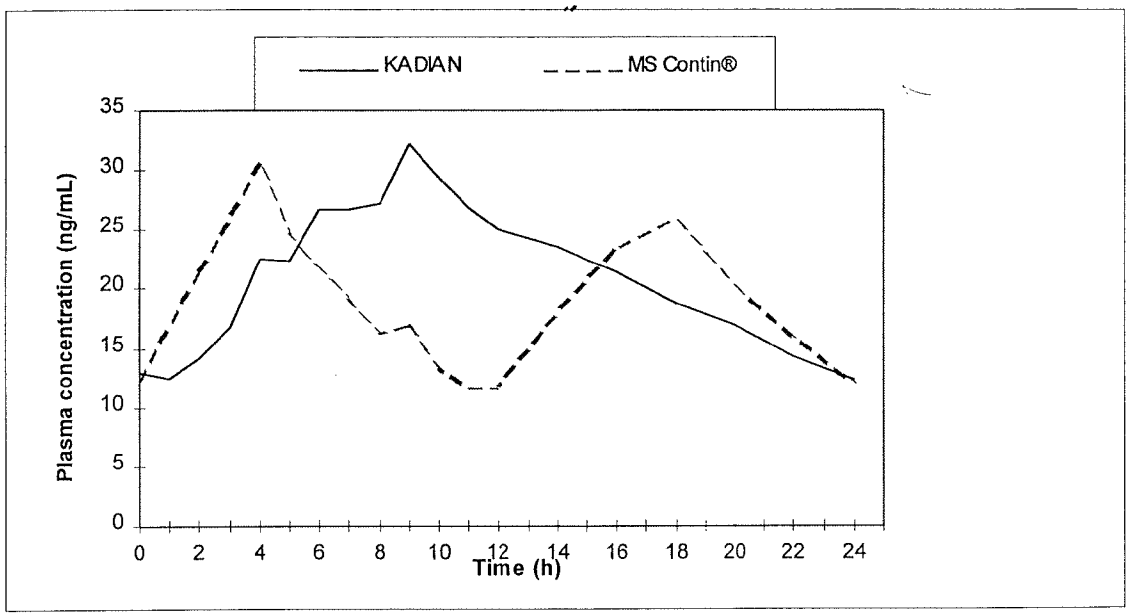
Steady State: When KADIAN™ is given on a fixed dosing regimen to patients with chronic pain due to malignancy, steady state is achieved in about two days. At steady state, KADIAN™ will have a significantly lower C_{max} and a higher C_{min} than equivalent doses of oral morphine solution and some other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

Graph 1 (Study # MOB-1/90): Mean steady state plasma morphine concentrations for KADIAN™ (twice a day), controlled-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) controlled-release morphine tablets (MS Contin®), 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, controlled-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 in the liver to produce glucuronides or with sulfuric acid to give morphine-3-etheral 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 controlled-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 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 children. The clearance of morphine and its elimination half-life begin to approach adult values by the second month of life. Children 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**).

Clinical Studies
A total of 177 healthy subjects and 337 patients with cancer pain participated in a total of 15 studies (10 pharmacokinetic and 6 clinical; one study reported both pharmacokinetic and clinical data). Of these individuals, 158 healthy subjects and 268 patients received KADIAN™. In the controlled clinical studies patients were followed for a median duration of 7 days and in the open label studies patients were followed for up to 12-24 months. KADIAN™ was compared to oral morphine solution and to either MS Contin® or to a 12-hour controlled-release morphine tablet bioequivalent to MS Contin® using trial designs that followed the clinical and pharmacokinetic performance of each treatment in cancer patients receiving chronic opioid therapy.

In two controlled studies, patients with moderate to severe cancer pain were titrated with immediate-release morphine (IRM) solution or tablets to a stable total daily dose of morphine for at least three consecutive days, then randomized to KADIAN™ or 12-hour controlled release morphine for seven days of observation. KADIAN™ given once a day proved similar to the same total dose of morphine given in divided doses in a 12-hour dosage form, with respect to pain relief, use of rescue medication, patient and investigator global assesment, and quality of sleep. Individual patient differences in the pattern of pain control emphasize the need to individualize both dose and dosing interval (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE
KADIAN™ is indicated for the management of moderate to severe pain where treatment with an opioid analgesic is indicated for more than a few days (see **CLINICAL PHARMACOLOGY; Clinical Studies**).

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

CONTRAINDICATIONS

KADIAN™ is contraindicated in patients with a known hypersensitivity to morphine, morphine salts or any of the capsule components.
KADIAN™ is contraindicated in patients with respiratory depression in the absence of resuscitative equipment, and in patients with acute or severe bronchial asthma.

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

WARNINGS

(See also **CLINICAL PHARMACOLOGY**)

Impaired Respiration

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

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve (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.

Head Injury and Increased Intracranial Pressure

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

Hypotensive Effect

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

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.

PRECAUTIONS
(See also **CLINICAL PHARMACOLOGY**)

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

Cordotomy
Patients 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.

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

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

1. KADIAN™ capsules should NOT be opened, chewed, crushed or dissolved. The pellets in KADIAN™ capsules should NOT be chewed, crushed or dissolved.

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

3. Morphine 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.

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

5. Women of childbearing potential who become or are planning to become pregnant, should consult a physician.

6. Upon completion of therapy, it may be appropriate to taper the morphine dose, rather than abruptly discontinuing it.

7. While psychological dependence ("addiction") to morphine used in the treatment of pain is very rare, morphine is one of a class of drugs known to be abused and should be handled accordingly.

8. As with other opioids, patients taking KADIAN™ should be advised that severe constipation could occur and appropriate laxatives, stool softeners and other appropriate treatments should be initiated from the beginning of opioid therapy.

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

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

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. We do not recommend the use of Kadian 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.

Food: The bioavailability of KADIAN™ is not significantly affected by food. KADIAN™ Capsules should be swallowed whole. The capsules, as well as the pellets contained in the capsules, however, must not be crushed, chewed, or mixed with food due to risk of overdose (see **DOSAGE AND ADMINISTRATION,** and **INFORMATION FOR PATIENTS**)

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 lethal 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 high 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 to 3-fold the maximum recommended human dose (MRHD) on a mg/m^2 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 skill 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.

Morphine should only be used during pregnancy if the need for strong opioid analgesia justifies the potential 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