KADIAN- morphine sulfate capsule, extended release
Bryant Ranch Prepack

KADIAN

BOXED 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.

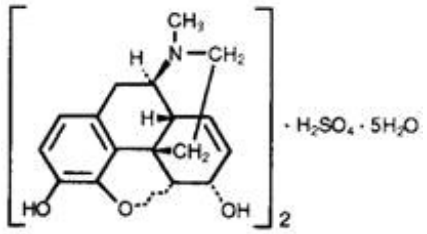
KADIAN® Capsules are NOT for use as a prn analgesic.

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 10 mg, 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_b is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4).

Each KADIAN® extended-release capsule contains either 10 mg, 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 red #28, FD&C blue #1 (10 mg), 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#,+ (ng.h/mL)	C_{max}+ (ng/mL)	T_{max} (h)	C_{min}+ (ng/mL)	Fluctuation*
Single Dose (n=24)					
KADIAN® Capsule	271.0 (19.4)	15.6 (24.4)	8.6 (41.1)	na^	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 (55.8)	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)
Extended-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 = C_{max}- C_{min}/C_{min}

^ Not applicable

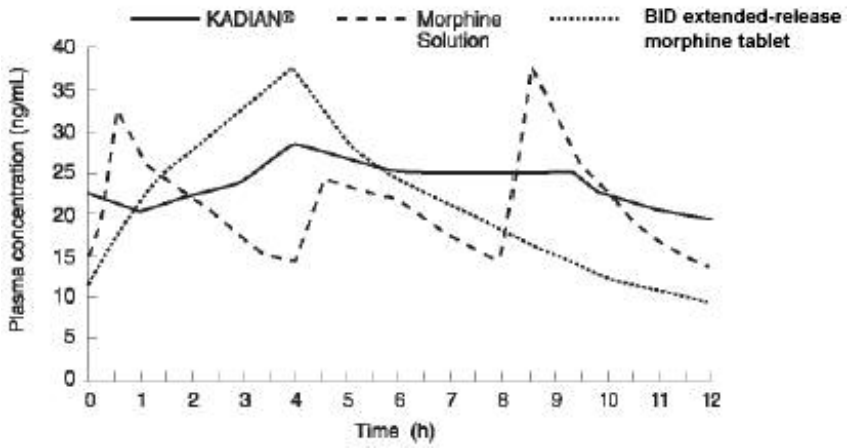
Absorption

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.

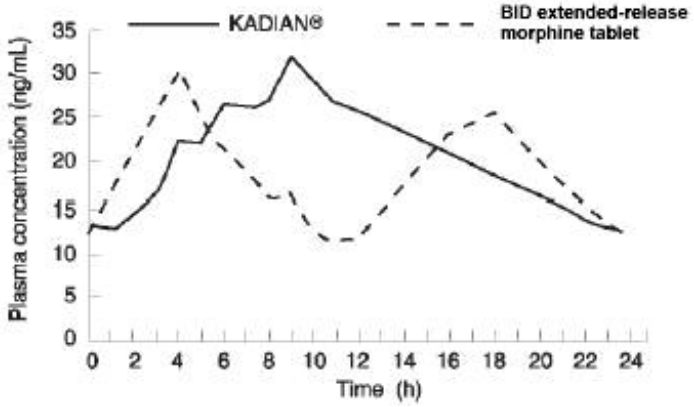
Steady State: When KADIAN® is given on a fixed dosing regimen to patients with chronic pain due to malignancy, steady state is achieved in about two days. At steady state, KADIAN® will have a significantly lower C_{max} and a higher C_{min} than equivalent doses of oral morphine solution and some other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

Graph 1 (Study # MOB-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 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 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 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.

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.

Carcinogenesis, Mutagenesis, 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 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 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. KADIAN® 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 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 coexposes 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 used (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 opioid 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, pallor, facial flushing, palpitations, bradycardia, syncope

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

Endocrine: Hyponatremia due to inappropriate ADH secretion, gynecomastia

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

Hemic & Lymphatic: Anemia, leukopenia, thrombocytopenia

Metabolic & Nutritional: Peripheral edema, hyponatremia, edema

Musculoskeletal: Back pain, bone pain, arthralgia

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

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

Special Senses: Amblyopia, conjunctivitis, miosis, blurred vision, nystagmus, diplopia

Urogenital: Urinary abnormality, amenorrhea, urinary retention, urinary hesitancy, 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 no 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 reluctance 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 before 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. 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 patients 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 10 mg or 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 this 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 wet.

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 no 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), <u>then halve this dose as an initial trial.</u>

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.

Kadian ER 20mg(CII) Capsule

KADIAN

morphine sulfate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:63629-4191(NDC:46987-322)
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
MORPHINE SULFATE (MORPHINE)	MORPHINE SULFATE	20 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSES	
ETHYLCELLULOSES	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1)	

POLYETHYLENE GLYCOLS	
DIETHYL PHTHALATE	
TALC	
STARCH, CORN	
SUCROSE	
GELATIN	
SILICON DIOXIDE	
SODIUM LAURYL SULFATE	
TITANIUM DIOXIDE	
D&C YELLOW NO. 10	

Product Characteristics

Color	YELLOW	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	Kadian;20;mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-4191-1	60 in 1 BOTTLE		
2	NDC:63629-4191-2	30 in 1 BOTTLE		
3	NDC:63629-4191-3	90 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020616	04/07/2009	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-4191), RELABEL(63629-4191)