

# KADIAN® Morphine Sulfate Sustained Release Capsules



## Brief Summary

### 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 **DOSE AND ADMINISTRATION**.

#### Concomitant

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 overdosage or withdrawal syndromes.

#### Use in Pancreatic/Biliary Tract Diseases

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 be swallowed whole (not chewed, crushed, or dissolved). Alternatively, KADIAN® capsules may be opened and the entire contents sprinkled on a small amount of applesauce immediately prior to ingestion. The pellets should NOT be chewed, crushed, or dissolved due to risk of overdose. When prescribing KADIAN®, by the sprinkle method, details of proper technique should be explained to the patient. KADIAN® capsules may also be opened and the entire contents sprinkled over about 10 mL of water in a beaker then flushed with swirling through a pre-wetted 16-French gastrostomy tube fitted with a plastic funnel at the port end. The beaker is rinsed with additional aliquots of water as necessary to transfer all of the pellets to flush the tube. **NASOGASTRIC TUBES SHOULD NOT BE USED.** (Also see **DOSE AND ADMINISTRATION**.)
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, antiepileptics, 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.

**Monamine Oxidase Inhibitors (MAOIs):** MAOIs have been reported to intensify the effects of opioid drugs 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:** KADIAN® capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternatively, KADIAN® capsules may be opened and the entire contents sprinkled on a small amount of applesauce immediately prior to ingestion. The pellets in KADIAN® should NOT be chewed, crushed, or dissolved due to risk of overdose. (See **DOSE 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 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<sup>2</sup> 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<sub>2</sub> 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 is not consistent and may be offset by an increased rate of cervical dilation 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 paragon 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

There are studies from the literature reporting the safe and effective use of both immediate and sustained release oral morphine preparations for analgesia in pediatric patients who were dosed on a per kilogram basis. However, the safety of KADIAN®, both the entire capsule and the pellets sprinkled on applesauce, 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 applesauce sprinkling method is not an appropriate alternative for these patients.

#### 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, 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 morphine 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 morphine 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 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 controlled clinical trials in patients with chronic cancer pain the most common adverse events reported by patients at least once during therapy were drowsiness (9%), constipation (8%), nausea (7%), dizziness (6%), and anxiety (6%). Other less common side effects expected from morphine or seen in less than 3% of patients in the clinical trials 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, hyperesthesia, slurred speech, hallucinations, vasodilation, euphoria, apathy, seizures, myoclonus

**Endocrine:** Hyponatremia due to inappropriate ADH secretion, gynecostasia

**Gastrointestinal:** Vomiting, anorexia, dysphagia, dyspepsia, diarrhea, abdominal pain, stomach atony disorder, gastroesophageal 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

#### DRUG ABUSE AND DEPENDENCE

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

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

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

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

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

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

KADIAN® has no role in the management of opioid addiction.

#### 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 a sustained release formulation such as KADIAN® has been taken. Care should be taken to secure the airway before attempting treatment by gastric emptying or activated charcoal.

The pure opioid 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.

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

#### Rx only

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