PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]KADIAN®

morphine sulphate pentahydrate

Morphine Sulphate Sustained Release Capsules
10 mg, 20 mg, 50 mg and 100 mg
Oral

Manufacturer's Standard

Opioid Analgesic

BGP Pharma.ULC
85 Advance Road
Etobicoke, Ontario
M8Z 2S6

Date of Initial Approval:
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RECENT MAJOR LABEL CHANGES

Serious Warnings and Precautions (3); DOSAGE AND ADMINISTRATION (4); WARNINGS AND PRECAUTIONS (7), Endocrine and Metabolism; Neurologic; Sexual Health. ADVERSE REACTIONS (8), Post-Market Adverse Reactions (8.2). DRUG INTERACTIONS (9), Drug-Drug Interactions (9.1). PATIENT MEDICATION INFORMATION. MAR 2018

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KADIAN® is indicated in adults for:

- Management of pain severe enough to require daily, continuous, long-term opioid treatment, and:
  - that is opioid-responsive; and
  - for which alternative options are inadequate.

- KADIAN® is not indicated as an as-needed (prn) analgesic.

1.1 Pediatrics

Pediatrics (**<18 years of age):** The safety and efficacy of KADIAN® has not been studied in the pediatric population. Therefore, the use of KADIAN® is not recommended in patients under 18 years of age.

1.2 Geriatrics

Geriatrics (>65 years of age): 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, concomitant disease or other drug therapy.

2 CONTRAINDICATIONS

KADIAN® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

KADIAN® is also contraindicated:

- In patients who are hypersensitive to other opioid analgesics.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- In patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- In patients with mild, intermittent or short duration pain that can be managed with other pain medications.
- The management of acute pain.
- Patients with acute asthma or other obstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients with toxic psychosis and severe kyphoscoliosis.

- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery (see **Serious Warnings and Precautions** and **WARNINGS AND PRECAUTIONS**).
- Patients who consume alcohol, or any medication containing alcohol. Co-ingestion of KADIAN® and alcohol can potentially result in rapid increases in opioid plasma concentrations which may be fatal, even in opioid tolerant patients.
- Patients with cardiac arrhythmias.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, KADIAN® should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids) (see DOSAGE AND ADMINISTRATION).**
- **Addiction, Abuse, and Misuse: KADIAN® poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing KADIAN®, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). KADIAN® should be stored securely to avoid theft or misuse**.
- **Life-threatening Respiratory Depression: OVERDOSE**
  Serious, life-threatening, or fatal respiratory depression may occur with use of KADIAN®. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of KADIAN® or following a dose increase. Instruct patients to swallow KADIAN® capsules whole or to sprinkle the contents of the capsule on applesauce or custard and swallow immediately without chewing. Cutting, breaking, crushing, chewing, or dissolving KADIAN® can lead to rapid release and absorption of a potentially fatal dose of morphine sulphate (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.
- **Accidental Exposure: Accidental consumption of even one dose of KADIAN®, especially by children, can result in a fatal overdose of morphine (see DOSAGE AND ADMINISTRATION subsection Disposal, for instructions on proper disposal).**
- **Neonatal Opioid Withdrawal Syndrome: Prolonged maternal use of KADIAN® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).**
- **Interaction with Alcohol: The co-ingestion of alcohol with KADIAN® should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).**
- **Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants: Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma,**

and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of KADIAN® and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 90 mg of KADIAN® not be exceeded. Each patient should be assessed for their risk prior to prescribing KADIAN®, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of KADIAN® (see DOSAGE AND ADMINISTRATION, Adjustment or reduction of Dosage).**
- **KADIAN® should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids).**
- **KADIAN® should be swallowed whole; crushing, chewing, or dissolving KADIAN® can cause rapid release and absorption of a potentially fatal dose of morphine sulphate (see WARNINGS AND PRECAUTIONS).**

4.2 Recommended Dose and Dosage Adjustment

KADIAN® capsules are to be administered once daily (every 24 hours).

Selection of the initial dose of KADIAN® should take into account the following:

i) the total daily dose, potency and characteristics of previous opioid analgesics (e.g., pure agonists or mixed agonist/antagonist.)

ii) the reliability of the relative potency estimate used to calculate the dose of morphine required (potency estimates vary with the route of administration).

iii) the degree of opioid tolerance.

iv) the patient's general condition and medical status.

v) type and severity of pain.

Individual dosing requirements vary considerably based on each patient's size, weight, severity

of pain, and medical and analgesic history.

Patients over the age of 50 tend to require much lower doses of morphine than do younger patients. In elderly and debilitated patients and those with impaired respiratory function or significantly decreased renal function, the initial dose should be one half of the usual recommended dose.

The use of opioid analgesics for the relief of chronic pain, including cancer pain, should be only part of a complete approach to pain control which should include other types of treatment or drug therapy, non-drug measures and psychosocial support.

If signs of excessive opioid effects are observed early in the dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, breakthrough pain occurs, a supplemental dose of a short acting analgesic may be given. If breakthrough pain repeatedly occurs at the end of a dose interval, it is generally an indication for dosage increase, not more frequent administration. However, where judged necessary, KADIAN® may be administered more frequently than every 24 hours. The dosing interval of KADIAN® should not be reduced below every 12 hours. As experience is gained, adjustments can be made to obtain an appropriate balance between pain relief and opioid side effects.

For essential information on the important details of the management of cancer pain, the reader may wish to consult the following resources:

Paice JA, et al. Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016; 34(27):3325-45.

National Comprehensive Cancer Network (NCCN). Adult cancer pain. J Natl Compr Canc Netw. 2013; 11(8):992-1022.

Because of the sustained release properties of KADIAN®, dosage increases should generally be separated by 48 hours.

When properly ingested, no evidence of dose dumping was observed in any of the patients receiving their full daily dose of morphine in the q24h arms of the various steady-state studies.

Use of KADIAN® as the First Opioid Analgesic: There has been no systematic evaluation of KADIAN® as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient using a controlled release morphine, it is ordinarily advisable to begin treatment using an immediate release formulation.

For patients currently receiving opioids, the following dosing recommendations should be considered.

Conversion from Immediate Release Oral Morphine Formulations to KADIAN®: Patients on immediate release oral morphine formulations may be converted to KADIAN® by administering the patient's total daily morphine dose as KADIAN® capsules on an every 24 hours dosing regimen. Dose is then adjusted as needed.

The first dose of KADIAN® should be taken with the last dose of any immediate-release opioid medication due to the prolonged T_{max} after administration of KADIAN®.

Conversion from Sustained-Release Oral Morphine Formulations to KADIAN®: Patients on sustained-release oral morphine formulations may be converted to KADIAN® by administering the patient's total daily morphine dose as KADIAN® capsules on an every 24 hours dosing regimen at the time of the next scheduled dose of morphine.

Conversion from Parenteral Morphine or Other Parenteral or Oral Opioids to KADIAN®: If KADIAN® is administered as the initial oral morphine drug product, particular care must be exercised in the conversion process. Because of uncertainty about an inter subject variation in relative estimates of opioid potency and cross tolerance, initial dosing regimens should be conservative; that is, an underestimation of the 24 hours' oral morphine requirements is preferred to an overestimate. To this end, initial individual doses of KADIAN® should be estimated conservatively.

Estimates of the relative potency of opioids are only approximate and are influenced by route of administration, individual patient differences, and possibly, by an individual's medical condition.

Consequently, it is difficult to recommend any fixed rule for converting a patient to KADIAN® directly. The following general points should be considered:

Parenteral to Oral Morphine Ratio: Estimates of the oral to parenteral potency of morphine vary. Some authorities suggest that a dose of oral morphine only two to three times the daily parenteral morphine requirement may be sufficient in chronic use settings.

Other Parenteral or Oral Opioids to Oral Morphine: Because there are no data on these types of analgesic substitutions, specific recommendations are not possible. Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate (see Table 1). In general, it is safer to underestimate the daily dose of KADIAN® required and rely upon ad hoc supplementation to deal with inadequate analgesia.

Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, consider reducing the calculated dose by 25-50% to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

TABLE 1: Opioid Conversion Table[a]

Opioids	To convert to oral morphine equivalent	To convert from oral morphine multiply by	Daily 90 mg MED[b]
Morphine	1	1	90 mg/d
Codeine	0.15	6.67	600 mg/d
Hydromorphone	5	0.2	18 mg/d
Oxycodone	1.5	0.667	60 mg/d
Tapentadol	0.3-0.4	2.5-3.33	300 mg/d
Tramadol	0.1-0.2	6	***
Methadone	Morphine dose equivalence is not reliably established		

*** The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.
a.Adapted from the 2017 Canadian guideline for opioids for chronic non-cancer pain. McMaster University; 2017
b.MED: Morphine Equivalent Dose

Conversion from KADIAN® to Other Controlled Release Oral Morphine Formulations:
KADIAN® is not bioequivalent to other controlled release morphine preparations. Conversion from KADIAN® to the same daily dose of other controlled-release morphine preparations may lead to an initial change in the clinical status of the patient and close observation is recommended.

Conversion from KADIAN® to Parenteral Opioids: When converting a patient from KADIAN® to parenteral opioids, it is best to assume that the parenteral to oral potency is high. NOTE THAT THIS IS THE CONVERSE OF THE STRATEGY USED WHEN THE DIRECTION OF CONVERSION IS FROM THE PARENTERAL TO ORAL FORMULATIONS. IN BOTH CASES HOWEVER, THE AIM IS TO ESTIMATE THE NEW DOSE CONSERVATIVELY. For example, to estimate the required 24 hour dose of morphine for IM use, one could employ a conversion of 1 mg of morphine IM for every 6 mg of morphine as KADIAN®. Therefore, the IM 24 hour dose would have to be divided by six and administered every 4 hours. This approach is recommended because it is least likely to cause overdose. However, for chronic dosing, clinical experience indicates that this ratio is 2-3:1 and individual titration is recommended (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).

Opioid analgesic agents do not effectively relieve dysesthetic pain, post herpetic neuralgia, stabbing pains, activity related pain, and some forms of headache. This does not mean that patients with advanced cancer suffering these types of pain should not be given an adequate trial of opioid analgesics. However, such patients may need to be referred early on for other types of pain therapy. Pain without nociception is usually not opioid responsive.

Dose Titration: Dose titration is the key to success with morphine therapy. Proper optimization of doses scaled to the relief of the individual's pain should aim at the regular administration of the lowest dose of morphine which will maintain the patient free of pain at all times. Dose adjustments should be based on the patient's clinical response. Higher doses may be justified in some patients to cover periods of physical activity.

Because of the sustained release properties of KADIAN®, dosage adjustments should generally be separated by 48 hours. If dose increments turn out to be required, they should be proportionately greater at lower dose levels (in terms of percentage of the previous dose), than when adjusting a higher dose.

Adjustment or Reduction of Dosage: Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including KADIAN®. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

During the first 2 or 3 days of effective pain relief, the patient may exhibit drowsiness or sleep for prolonged periods. This can be misinterpreted as the effect of excessive analgesic dosing rather than the first sign of relief in a pain-exhausted patient. The dose, therefore, should be maintained for at least 3 days before reduction, provided that the sedation is not excessive or associated with unsteadiness and symptoms of confusion, and that respiratory activity and other vital signs are adequate. If excessive sedation persists, the reason(s) for such an effect must be sought. Some of these are concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated by an older patient, or an illness which is more severe than previously recognized. If it is necessary to reduce the dose, it can be carefully increased again after 2 or 4 days if it is obvious that the pain is not being well-controlled.

Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualized and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Pediatrics (< 18 years of age)
The safety and efficacy of KADIAN® has not been studied in the pediatric population. Therefore, the use of KADIAN® is not recommended in patients under 18 years of age.

Geriatrics (> 65 years of age)
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, concomitant disease or other drug therapy.

4.3 Administration

KADIAN® should be swallowed whole; crushing, chewing, or dissolving Kadian can cause rapid release and absorption of a potentially fatal dose of morphine sulphate (see **WARNINGS AND PRECAUTIONS**).

For patients who have difficulty swallowing, KADIAN® capsules may be opened and the sustained-release pellets may be administered in the following way:

- The pellets may be sprinkled onto a small amount of soft foods (such as yoghurt, apple sauce or jam). This should be taken within 30 minutes of sprinkling. The pellets must not be chewed or crushed, and the mouth should be rinsed to ensure that all pellets have been swallowed.

4.4 Missed Dose

If a dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, then the missed one should be skipped. Two doses should not be taken at once. If several doses are missed, then patients should contact their physician.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

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

Treatment: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonist, naloxone hydrochloride, is a specific antidote against respiratory depression which results from opioid overdose. Naloxone (usually 0.4 to 2.0 mg) should be administered intravenously. However, because its duration of action is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re established. KADIAN® will continue to release and add to the morphine load for periods longer than the action of a single dose of antagonist and the management of morphine overdosage should be modified accordingly. If the response to naloxone is suboptimal or not sustained, additional naloxone may be administered as needed, or given by continuous intravenous infusion to maintain alertness and respiratory function. There is no information available about the cumulative dose of naloxone that may be safely administered.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdosage. Naloxone should be administered cautiously to persons who are known or suspected to be physically dependent on KADIAN®. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If it is necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

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

Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a sustained release formulation has been taken.

Morphine toxicity may be a result of overdosage but because of the large inter individual variation in sensitivity to opioids it is difficult to assess the exact dose of any opioid that is toxic or lethal. The toxic effects of morphine tend to be overshadowed by the presence of pain or tolerance. Patients having chronic morphine therapy have been known to take in excess of 3,000 mg/day with no apparent toxic effects being present.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules, 10 mg, 20 mg, 50 mg and 100 mg	Diethyl Phthalate, Ethylcellulose N-50, Gelatin, Hypromellose, Methacrylic Acid Copolymer (Type C), Polyethylene Glycol 6000 (Macrogol 6000), Purified Talc, Sugar Spheres (16-18 mesh), and a black ink containing: ammonium hydroxide, the colouring agent E172 (black iron oxide), potassium hydroxide, propylene glycol, and shellac

KADIAN® capsules contain creamy-white to light tan polymer coated sustained release pellets of morphine sulphate pentahydrate and are available in four dosage strengths.

- **10 mg morphine sulphate pentahydrate:** Size 4 capsule, clear cap imprinted with K10, and clear body imprinted with one black band. Presented in white plastic bottles of 100 capsules.

- **20 mg morphine sulphate pentahydrate:** Size 4 capsule, clear cap imprinted with K20, and clear body imprinted with two black bands. Presented in white plastic bottles of 100 capsules.

- **50 mg morphine sulphate pentahydrate:** Size 2 capsule, clear cap imprinted with K50, and clear body imprinted with three black bands. Presented in white plastic bottles of 100 capsules.

- **100 mg morphine sulphate pentahydrate:** Size 0 capsule, clear cap imprinted with K100, and clear body imprinted with four black bands. Presented in white plastic bottles of 50 capsules.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

KADIAN® is intended for use in patients who require more than several days of continuous treatment with a potent opioid analgesic.

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

Cordotomy

Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive KADIAN® within 24 hours of the procedure.

Cardiovascular

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 anaesthetics (see **DRUG INTERACTIONS**). KADIAN® may produce orthostatic hypotension in ambulatory patients.

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

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of KADIAN® and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opiate receptors to chronic exposure to an opiate, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

If treatment of physical dependence of patients on KADIAN® is necessary, detoxification may be achieved by a gradual dosage reduction. Gastrointestinal disturbance or dehydration should be treated appropriately.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. (see **DOSAGE AND ADMINISTRATION**, **Adjustment or Reduction of Dosage**). Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose,

sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS**, **Post-Market Adverse Reactions**).

Abrupt cessation or a sudden reduction in dose after prolonged use may result in withdrawal symptoms. The opioid agonist abstinence syndrome is characterized by some or all of the following symptoms: restlessness, lacrimation, rhinorrhea, yawning, perspiration, gooseflesh, restless sleep or "yen" and mydriasis during the first 24 hours. These symptoms often increase in severity and over the next 72 hours may be accompanied by increasing irritability, anxiety, weakness, twitching and spasms of muscles, kicking movements, severe backache, abdominal and leg pains, abdominal and muscle cramps, hot and cold flashes, insomnia, nausea, anorexia, vomiting, intestinal spasm, diarrhea, coryza and repetitive sneezing, increase in body temperature, blood pressure, respiratory rate and heart rate. Because of excessive loss of fluids through sweating, vomiting and diarrhea, there is usually marked weight loss, dehydration, ketosis and disturbances in acid base balance. Cardiovascular collapse can occur. Most observable symptoms disappear in 5-14 days without treatment; however, there appears to be a phase of secondary or chronic abstinence which may last for 2-6 months characterized by insomnia, irritability and muscle aches.

Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, may develop upon repeated administration of morphine. The dose of KADIAN® may need to be increased to maintain adequate pain relief (see **DOSAGE AND ADMINISTRATION**).

Use in Drug and Alcohol Addiction:
KADIAN® is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore KADIAN® should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as KADIAN®, should be used with particular care in patients with a history of alcohol and illicit/ prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to KADIAN® unless used under extreme caution and awareness.

Endocrine
Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being

more likely to be associated with adrenal insufficiency.

Driving and Operating Machinery
Due caution should be exercised when driving or operating a vehicle or potentially dangerous 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, sedative/hypnotics and alcohol (see **DRUG INTERACTIONS**).

Gastrointestinal
Gastrointestinal Motility
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 any other solid dose morphine formulation, diarrhea may reduce morphine absorption.

Neurologic
Interactions with Central Nervous System (CNS) Depressants (Including benzodiazepines and alcohol)
KADIAN® should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. KADIAN® should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see **DRUG INTERACTIONS**).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when KADIAN® is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and

warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

KADIAN® should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**, **Sedation**, and **DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

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 neurological signs of further increases in pressure in patients with head injuries. KADIAN® is contraindicated in patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of KADIAN® is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Use in Patients with Convulsive or Seizure Disorders
The morphine sulphate in KADIAN® may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Therefore, KADIAN® should not be used in these patients (see **CONTRAINDICATIONS**).

Serotonin Syndrome
KADIAN® could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. KADIAN® should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

Respiratory
Respiratory Depression
Serious, life-threatening, or fatal respiratory depression has been reported with the use of

opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of KADIAN®, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with KADIAN® and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of KADIAN® are essential (see **DOSAGE AND ADMINISTRATION**). Overestimating the KADIAN® dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Sexual Health
Sexual Function/Reproduction
Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**).

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproduction studies have not been performed using morphine. It is not known whether morphine can cause foetal damage when administered throughout pregnancy or if it can affect reproductive capacity in humans.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS** – Neonatal Opioid Withdrawal Syndrome).

Use of KADIAN® is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Labour, Delivery and Nursing Women
KADIAN® is contraindicated during labour, delivery, pregnancy and in nursing mothers. Morphine sulphate can cross the placental barrier and is also excreted in breast milk. Life-threatening respiratory depression may occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if KADIAN® is used in this population.

7.1.2 Pediatrics

Pediatrics < 18 years of age: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.3 Geriatrics

Geriatric and/or Debilitated Patients

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

Most common adverse effects are: constipation, dizziness, dysphoria, euphoria, lightheadedness, nausea, sedation, sweating and vomiting.

8.2 Post-Market Adverse Reactions

Sedation:
Most patients receiving morphine will experience initial drowsiness. This usually disappears in three to five days and is not a cause for concern unless it is excessive, or accompanied with unsteadiness or confusion. Excessive or persistent sedation should be investigated. Factors to be considered should include concurrent sedative medications, the presence of hepatic or renal insufficiency, exacerbated respiratory failure, tolerance to the dose used especially in older patients, disease severity and the patient's general condition. If the dose of KADIAN® has been reduced and pain is not adequately controlled, the dose may be carefully increased again after a few days.

Dizziness and Unsteadiness:
May be associated with morphine induced postural hypotension, particularly in elderly or debilitated patients. The dosage should be adjusted according to individual needs but, because of reduced clearance, dosage may be lower in patients over 50 years of age.

Nausea and Vomiting:
Nausea and vomiting are common after single doses of morphine or as an early undesirable effect of regular opioid therapy. The prescription of a suitable antiemetic should be considered. The frequency of nausea and vomiting usually decreases within a week or so but may persist due to opioid induced gastric stasis.

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

Cardiovascular:
- Bradycardia
- Chills
- Faintness
- Flushing of the face

- Hypertension
- Hypotension
- Palpitations
- Syncope
- Tachycardia

Central Nervous System (CNS):
- Agitation
- Alterations in mood (nervousness, apprehension, depression, floating feelings)
- Confusional symptoms and occasionally hallucinations
- Disorientation
- Dizziness
- Dysphoria
- Dyspnea
- Euphoria
- Headache
- Hypothermia
- Increased intracranial pressure
- Insomnia
- Muscle rigidity
- Paresthesia
- Seizures
- Serotonin syndrome
- Tremor
- Uncoordinated muscle movements
- Weakness

Gastrointestinal:
- Anorexia
- Biliary colic
- Colic
- Constipation
- Dry mouth
- Laryngospasm
- Taste alterations

Genitourinary:
- Reduced libido or potency
- Urine retention or hesitancy

Endocrine:
- Androgen deficiency
- A syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatraemia secondary to decreased free water excretion may occur (monitoring of electrolytes may be necessary).

Visual Disturbances:
- Blurred vision
- Diplopia

- Miosis
- Nystagmus

Dermatologic:
- Diaphoresis
- Oedema
- Other skin rashes
- Pruritus
- Urticaria

Withdrawal (Abstinence) Syndrome:
Chronic use of opioid analgesics may be associated with the development of physical dependence. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered.

Withdrawal symptoms that may be observed after discontinuation of opioid use include body aches, diarrhea, piloerection, anorexia, nervousness or restlessness, rhinorrhea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbance, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.

Androgen deficiency:
Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Cimetidine		There is a report of confusion and severe respiratory depression when a haemodialysis patient was administered morphine and cimetidine.	

Central Nervous System (CNS) Depressants (including benzodiazepines and alcohol)		Risk of respiratory depression, hypotension and profound sedation or coma.	Morphine should be used with great caution and in reduced dosage in patients concurrently receiving other central nervous system depressants including sedatives, hypnotics, general anaesthetics, phenothiazines and other tranquilizers. Co-ingestion of KADIAN® and alcohol is contraindicated since it can potentially result in rapid increases in opioid plasma concentrations which may be fatal, even in opioid tolerant patients. When such combined therapy is contemplated, the dose of one or both agents should be reduced.
Diuretics		Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.	
Mixed Agonist/Antagonist Opioid Analgesics	T	Mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.	Mixed agonist/antagonist opioid analgesics (e.g., pentazocine and buprenorphine) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic.
Monoamine Oxidase Inhibitors (MAOIs)		The concurrent use of MAOIs and other opioid drugs such as morphine can cause anxiety, confusion and significant depression of respiration, sometimes leading to coma.	Morphine should not be given to patients taking MAOIs or within 14 days of stopping such treatment.

Muscle Relaxants		Morphine may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression.	
Serotonergic Agents (including SSRIs, SNRIs, tricyclic antidepressants, MAOIs, other psychiatric medications [amoxapine, maprotiline, nefazodone, trazodone, buspirone, vilazodone, mirtazapine and lithium], migraine medicines [5-HT_1 agonists), antiemetics [ondansetron, granisetron, dolasetron, palonosetron] and other serotonergic medications [including dextromethorphan, linezolid, cyclobenzaprine, methylene blue, St. John's Wort, tryptophan].		Coadministration of morphine sulphate with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS, Neurologic**). This may occur within the recommended dose range. Symptoms of serotonin syndrome may include mental status changes such as agitation, hallucinations, or coma; autonomic instability such as tachycardia, labile blood pressure, or hyperthermia; and neurologic abnormalities such as hyperreflexia, incoordination, or rigidity. The onset of symptoms generally occurs within several hours to a few days of concomitant use but may occur later, particularly after dose increases.	If concomitant use of morphine with a serotonergic drug is warranted, the patient should be observed for symptoms of serotonin syndrome, particularly during treatment initiation and dose increases. Treatment with the opioid and/or serotonergic medication should be discontinued if serotonin syndrome is suspected, and the patient should receive immediate medical attention.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.2 Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see **SERIOUS WARNINGS AND PRECAUTIONS** Box).

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Morphine is an opiate agonist. Its principal pharmacologic effect is exerted on the CNS and on the intestines. Morphine interacts as an agonist at specific receptor binding sites and is a more potent agonist at the u-receptor (localized in pain modulating regions of the CNS) than at the k-receptor (localized in the deep layers of the cerebral cortex). Analgesia, miosis, and/or decreased body temperature can result from agonist activity at the u- or k-receptor. The opiate agonists act at several sites within the CNS. This action involves several systems of neurotransmitters to produce analgesia, the precise mechanism of which has not been fully elucidated. Threshold or responsiveness of afferent nerve endings to noxious stimuli and the conduction of impulses along peripheral nerves are not altered by opiate agonist activity. Instead, the drugs alter pain perception at the spinal cord and higher levels in the CNS. The patient's emotional response to pain is also altered.

Morphine is an opioid analgesic which exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. Morphine produces diverse pharmacological effects in man including analgesia, suppression of the cough reflex, respiratory depression due to a reduction in the responsiveness of the respiratory centre to carbon dioxide, nausea and emesis through direct stimulation of the chemoreceptor trigger-zone (CTZ), mood changes including euphoria and dysphoria, sedation, mental clouding, alterations in both the endocrine and autonomic nervous systems, and a decrease in gastrointestinal motility leading to constipation.

10.2 Pharmacodynamics

Opiate agonist activity on the CNS causes suppression of the cough reflex, respiratory depression, drowsiness, sedation, change in mood, euphoria, dysphoria, mental clouding, nausea, vomiting, and EEG changes in addition to analgesia. Anaesthesia is a result of higher than usual dosages of analgesic. Respiratory depression is produced by morphine by a direct effect on the respiratory centres in the brain stem. This results in decreased sensitivity and responsiveness to increases in serum carbon dioxide tension (PCO_2). Morphine decreases gastric, biliary, and pancreatic secretions and delays digestion. The precise action of clinical doses of opiate agonists on GI smooth muscle tone is controversial, however the ultimate result is constipation. Morphine increases smooth muscle tone in the antral portion of the stomach, the small intestine (particularly the duodenum), the large intestine, the sphincters and in the biliary and urinary tracts. Spasms (particularly of the sphincter of Oddi) and an increase in biliary tract pressure may also result.

10.3 Pharmacokinetics

Absorption: Oral administration of morphine results in good absorption. Morphine is rapidly absorbed from the gastrointestinal tract, nasal mucosa and lung after subcutaneous (SC) and intramuscular (IM) injection. When administered orally it is subject to extensive but variable 'first pass' metabolism and only about 40% of the administered dose reaches the central compartment.

Following oral administration, the dose normalised extent of absorption (AUC) of morphine from KADIAN® is similar to that obtained from morphine solutions. However, the rate of absorption of morphine from KADIAN® is significantly slower.

A single 50 mg oral dose of KADIAN® in 30 healthy male subjects resulted in a mean peak plasma morphine concentration of 8.1 ng/mL (C_{max}) at 8.5 hours (T_{max}). The extent of absorption was unaffected by food, but the T_{max} was slightly delayed to 10 hours. However, this is not clinically significant. KADIAN® can be administered with or without food.

Distribution: It is distributed in decreasing order of concentration into skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain. It easily penetrates the placental barrier and small amounts of morphine can be distributed into the milk of nursing women. About 30 to 35% of morphine is reversibly protein bound.

When KADIAN® is given on a fixed dosing regimen, steady state is achieved within about two days.

The pharmacokinetic characteristics of KADIAN® administered once daily for a 7 day period have been investigated in 24 patients with moderate-severe chronic cancer pain requiring opioid analgesia. The mean pharmacokinetic values were calculated from steady-state plasma morphine data and adjusted to a dose of 100 mg:

Parameter	**Mean ± S.D.**
C_{max} (ng/mL)	37.3 ± 14.0
T_{max} (h)	10.3 ± 3.3
AUC (ng.h/mL)	501 ± 193
C_{min} (ng/mL)	9.9 ± 5.2
T≥0.75 C_{max} (h)	6.0 ± 3.0

C_{max} = maximum observed plasma morphine concentration
T_{max} = time to reach Cmax
AUC = area under the plasma concentration time curve
C_{min}= minimum plasma morphine concentration
T≥0.75 C_{max} = time for which the plasma morphine concentration is greater than or equal to 75% of the C_{max}

Metabolism: Metabolism of morphine occurs principally in the liver. The drug undergoes conjugation with glucuronic acid at the 3-hydroxyl group, and secondary conjugation may also occur at the 6-hydroxyl group to form the 3, 6-diglucuronide.

Although a small fraction of morphine (less than 5%) is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites including morphine-3-glucuronide and morphine-6-glucuronide. The glucuronide system has very high capacity and is not easily saturated even in disease. Studies in healthy subjects and cancer patients have shown that the glucuronide metabolite to morphine mean molar ratios (based on AUC) are similar following single doses of KADIAN® and morphine sulphate solution. The morphine to morphine-3-glucuronide to morphine-6-glucuronide mean molar ratios (based on AUC) are approximately 1:26:4, similar to those occurring with morphine sulphate solution.

Elimination: Morphine is rapidly removed from the blood stream. Morphine has a mean elimination half-life of 2 to 3 hours. However, there is great inter-patient variability. Morphine is excreted in urine mainly as morphine-3-glucuronide and smaller amounts of morphine-3, 6-diglucuronide and unchanged drug (Morphine is excreted primarily in the urine as morphine-3-glucuronide and morphine-6-Glucuronide). A small amount of the glucuronide metabolites is excreted in the bile and there is some minor enterohepatic cycling.

Excretion in feces account for approximately 7-10% of a dose of morphine with a large portion of this excreted via the bile. Conjugated morphine which has been excreted in the bile may be hydrolysed and reabsorbed from the large bowel.

Morphine-6-glucuronide has been shown to be pharmacologically active. Because accumulation of this metabolite has been observed in patients with renal disease, caution should be exercised in patients with clinically significant impairment of renal function.

Special Populations and Conditions

Hepatic Insufficiency: There has been no evaluation of KADIAN® in patients with impaired hepatic function. Pharmacokinetic parameters of morphine show considerable inter-subject variation. The average volume of distribution (V_d) is approximately 4 L/kg and the terminal half-life is 2 to 4 hours.

Renal Insufficiency: There has been no evaluation of KADIAN® in patients with impaired renal function. Pharmacokinetic parameters of morphine show considerable inter-subject variation. The average volume of distribution (V_d) is approximately 4 L/kg and the terminal half-life is 2 to 4 hours.

11 STORAGE, STABILITY AND DISPOSAL

Store capsules between 15-25°C. Protect from light and moisture.

KADIAN® should be kept in a safe place, out of the sight and reach of children before, during and after use. KADIAN® should not be used in front of children, since they may copy these actions.

Unused or expired KADIAN® should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

KADIAN® should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

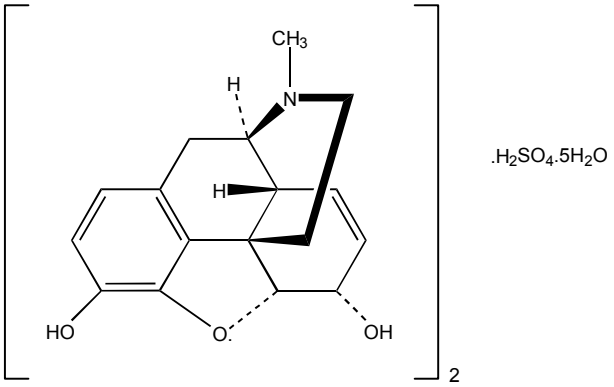
Drug Substance

Proper name: Morphine Sulphate pentahydrate

Chemical name: 7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol sulphate salt (2:1) pentahydrate

Molecular formula and molecular mass: $C_{34}H_{40}N_2O_{10}S \cdot 5H_2O$, 758.84

Structural formula:



Physicochemical properties:
Description: White crystalline powder consisting of acicular crystals or cubical masses.

Solubility: Soluble in water, very slightly soluble in alcohol, practically insoluble in toluene.

Specific Optical Rotation: -107° to -110°, determined on a 20 mg/mL aqueous solution, calculated with reference to the anhydrous, ethanol-free substance.

13 NON-CLINICAL TOXICOLOGY

There is considerable species to species variation in the acute toxicity of morphine in animal species. Patients receiving morphine may exhibit tolerance, psychological dependence, and physical dependence. Overdosage of morphine can cause respiratory depression and death even in patients who have developed tolerance. Physical dependence may result from continued administration of morphine which is closely related to tolerance. Miosis will usually continue to be exhibited by individuals who are morphine dependent. Withdrawal symptoms will result if morphine is abruptly discontinued or if an opiate antagonist is administered. If the patient has received 240 mg or more of morphine hydrochloride for 30 days or longer a severe abstinence syndrome occurs. Mothers who are physically dependent on opiate agonists will give birth to neonates who may also be opiate dependent. These neonates will usually exhibit withdrawal symptoms from 1 - 4 days after birth.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^{N}KADIAN®
Morphine Sulphate Sustained Release Capsules, Mfr. Std.
10 mg, 20 mg, 50 mg, 100 mg

Read this carefully before you start taking **KADIAN®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KADIAN®**.

Serious Warnings and Precautions

- **Even if you take KADIAN® as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., doctor).**

- **Life-threatening breathing problems can happen while taking KADIAN®, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**

- **Never give anyone your KADIAN®. They could die from taking it. If a person has not been prescribed KADIAN®, taking even one dose can cause a fatal overdose. This is especially true for children.**

- **If you took KADIAN® while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.

- **Taking KADIAN® with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is KADIAN® used for?
KADIAN® is used for the long-term management of pain, when:
- the pain is severe enough to require daily, around-the-clock medication.
- the doctor determines that other treatment options are not able to effectively manage your pain.

KADIAN® is NOT used ("as needed") to treat pain that you only have once in a while.

How does KADIAN® work?
KADIAN® is an oral sustained release capsule that slowly releases morphine sulphate over a 24-hour period.

KADIAN® contains morphine sulphate which is a pain medication belonging to the class of medicines known as opioids which also includes codeine, fentanyl and oxycodone. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in KADIAN®?
Medicinal ingredients: morphine sulphate pentahydrate
Non-medicinal ingredients: Diethyl Phthalate, Ethylcellulose N-50, Gelatin, Hypromellose, Methacrylic Acid Copolymer (Type C), Polyethylene Glycol 6000 (Macrogol 6000), Purified Talc, Sugar Spheres (16-18 mesh), and a black ink containing: ammonium hydroxide, the colouring agent E172 (black iron oxide), potassium hydroxide, propylene glycol, and shellac.

KADIAN® comes in the following dosage forms:
Capsules containing 10 mg, 20 mg, 50 mg or 100 mg morphine sulphate pentahydrate.
The 10 mg capsules are marked "K10" with one black band, the 20 mg capsules are marked "K20" with two black bands, the 50 mg capsules are marked "K50" with three black bands and the 100 mg capsules are marked "K100" with four black bands.

Do not use KADIAN® if:
- your doctor did not prescribe it for you
- you are allergic to morphine sulphate pentahydrate, other opioids, or any of the other ingredients of KADIAN®. You are reminded that KADIAN® contains sucrose and propylene glycol.
- you have mild or short-term pain that can be controlled by the occasional use of pain medication, including those available without a prescription.
- you have severe asthma, trouble breathing, or other lung problems.
- you have a condition where the small bowel does not work properly (paralytic ileus) or you have severe pain in your abdomen.
- you have gallbladder disease, bile duct disease or problems with your pancreas.
- you have a head injury
- you are at risk for seizures.
- you suffer from alcoholism.
- you have an irregular heartbeat.
- you are taking, or have taken within the past 2 weeks, a monoamine oxidase inhibitor medication (e.g., phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline).
- you are pregnant or plan to become pregnant, breast feeding, or in labour.
- you are under 18 years of age.
- you are going to have, or recently had, a planned surgery.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KADIAN®. Talk about any health conditions or problems you may have, including if you:
- have a history of illicit or prescription drug or alcohol abuse.
- have severe kidney, liver, lung disease.
- have heart disease.

- have low blood pressure.
- have past or current depression.
- suffer from chronic or severe constipation.
- have problems with your thyroid, adrenal or prostate gland.
- have inflammatory bowel disease or gallbladder disease.
- have problems with your pancreas.
- are going to have, or recently had, a planned surgery.
- have, or had in the past, hallucinations or other severe mental problems.
- suffer from migraines.

Other warnings you should know about:
Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery: Do not use KADIAN® while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. KADIAN® can then cause life-threatening breathing problems in your unborn baby or nursing infant.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to KADIAN®. KADIAN® can cause:
- drowsiness
- dizziness or
- light headedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:
- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off KADIAN®.

Serotonin Syndrome: KADIAN® can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take KADIAN® with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:
- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with KADIAN®:

- alcohol, including prescription and non-prescription medications containing alcohol. Do not drink alcohol while taking KADIAN®. This can lead to drowsiness, depressed breathing, unusually slow or weak breathing, serious side effects or a fatal overdose.
- other sedative drugs which may enhance the drowsiness caused by KADIAN®.
- other opioid analgesics (for pain).
- general anesthetics (used during surgery).
- drugs used to help you sleep or to reduce anxiety.
- antidepressants (for depression and mood disorders). Do not take KADIAN® with monoamine oxidase (MAO) inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with KADIAN®.
- psychiatric medications (such as amoxapine, maprotiline, nefazodone, trazodone, buspirone, vilazodone, mirtazapine and lithium).
- migraine medicines (5-HT1 agonists also called triptans).
- serotonergic medications (medicines that change the effect of serotonin in the body), such as dextromethorphan, linezolid, cyclobenzaprine, methylene blue, St. John's Wort and tryptophan.
- drugs used to treat serious mental or emotional disorders such as schizophrenia.
- antihistamines (for allergies).
- anti-emetics (for prevention of vomiting) such as ondansetron, granisetron, dolasetron, palonosetron.
- drugs used to treat muscle spasms and back pain.
- warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots).
- anti-retroviral, anti-fungal and antibiotic drugs.
- diuretics (water tablets).
- cimetidine (remedy for excess stomach acid).
- some heart medication (beta blockers).
- St. John's Wort.

How to take KADIAN®:

Take KADIAN®

- exactly as prescribed
- generally every 24 hours unless otherwise instructed by your doctor

KADIAN® can be swallowed whole or sprinkled on applesauce or custard.

Swallowed:

- swallow the capsule whole
- take the capsule with a full glass of water
- do not cut, break, chew, dissolve or crush the capsule - this can be dangerous and life threatening

Sprinkled:
- measure a tablespoon of warm or cold (4° - 40°C) applesauce or room temperature custard
- open the capsule
- sprinkle contents onto the tablespoon
- ensure the capsule is emptied of all contents
- take the entire tablespoon as soon as possible
- do not chew the contents (beads)
- rinse your mouth and swallow the water
- do not keep any of the food/medicine mixture for another dose

If you do not remember when you sprinkled the medicine on the applesauce or custard, or which food you sprinkled the medicine on, throw out the food/medicine mixture.

Do not take a single dose greater than 20 mg of KADIAN® every 24 hours unless you are "opioid tolerant". Your doctor will tell you when you are "opioid tolerant" to a certain dose of KADIAN®.

KADIAN® is not recommended for rectal administration.

Usual Adult Starting Dose:
Dosage is individualized. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor. Taking higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need KADIAN®. Be sure to use KADIAN® only for the condition for which it was prescribed.

Should your pain increase or any other complaint develop as a result of taking KADIAN®, tell your doctor immediately.

Stopping your Medication:
You should not stop taking KADIAN® all at once if you have been taking it for more than a few days.

Your doctor will monitor and guide you on how to slowly stop taking KADIAN®. You should do it slowly to avoid uncomfortable symptoms such as having:
- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble with sleeping
- an unusual increase in sweating

- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking KADIAN®.

Refilling Prescriptions for KADIAN®:
A new written prescription is required from your doctor each time you need more KADIAN®. Therefore, it is important that you contact your doctor before your current supply runs out.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

Overdose:

If you think you have taken too much KADIAN®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Signs of overdose may include:
- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:
It is important that you do not miss any doses. If you miss a dose, take your next dose at your usual time. You should always try to get back on track with your regular dosing schedule (for example, 8 o'clock in the morning or 8 o'clock in the evening). If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using KADIAN®?
These are not all the possible side effects you may feel when taking KADIAN®. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Confusion
- Constipation
- Dizziness
- Drowsiness
- Light-headedness
- Insomnia
- Nausea, vomiting, poor appetite, dry mouth
- Headache
- Problems with vision
- Weakness (lack of muscle strength), uncoordinated muscle movement

- Itching
- Sweating
- Difficulty in urinating
- Low sex drive, impotence (erectile dysfunction), infertility.

Talk with your doctor or pharmacist about ways to prevent constipation when you start using KADIAN®.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
Respiratory Depression: Slow, shallow or weak breathing.			√
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
Low Blood Pressure: dizziness, fainting, light-headedness.	√		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.
3 ways to report:

- Online at MedEffect: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html).

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep unused or expired KADIAN® in a secure place to prevent theft, misuse or accidental exposure.**
- Store at room temperature (15° - 25°C). Keep in a dry place.
- **Keep KADIAN® under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes KADIAN®, get emergency help right away.**

Disposal:
KADIAN® should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about KADIAN®:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), the manufacturer's website (www.mylan.ca), or by calling 1-844-596-9526.

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