KADIAN - morphine sulfate capsule, extended release
Bryant Ranch Prepack

HIGHLIGHTS OF PRESCRIBING INFORMATION
KADIAN® (morphine sulfate) Extended-Release Capsules, for oral use, CII
These highlights do not include all the information needed to use Kadian safely and effectively. See full prescribing information for Kadian.

Kadian (morphine sulfate) CAPSULE, EXTENDED RELEASE for ORAL use.
Initial U.S. Approval: 1941

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

See full prescribing information for complete boxed warning.

- **KADIAN contains pellets of morphine sulfate, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during KADIAN therapy. (5.1, 9)**
- **Fatal respiratory depression may occur, with highest risk at initiation and with dose increases. Instruct patients on proper administration of KADIAN capsules to reduce the risk. (5.2)**
- **Accidental ingestion of KADIAN can result in fatal overdose of morphine, especially in children. (5.3)**

RECENT MAJOR CHANGES

Boxed Warning	07/2012
Indications and Usage (1)	07/2012
Dosage and Administration (2)	07/2012
Contraindications (4)	07/2012
Warnings and Precautions (5)	07/2012

INDICATIONS AND USAGE

KADIAN is an opioid agonist product indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time (1)

Limitations of Use

- KADIAN is not for use:
- As an as-needed (prn) analgesic (1)
- For pain that is mild or not expected to persist for an extended period of time (1)
- For acute pain (1)
- For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time (1)
- KADIAN 100 mg, 130 mg, 150 mg, and 200 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established. (1)

DOSAGE AND ADMINISTRATION

Individualize dosing based on patient's prior analgesic treatment experience, and titrate as needed to provide adequate analgesia and minimize adverse reactions. (2.1, 2.2)
Instruct patients to swallow KADIAN capsules intact, or to sprinkle the capsule contents on applesauce and immediately swallow. (2.4)
Do not abruptly discontinue KADIAN in a physically dependent patient. (2.3, 5.11)

DOSAGE FORMS AND STRENGTHS

Capsules: 10 mg, 20 mg , 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, 200 mg (3)

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus (4)
- Hypersensitivity to morphine (4)

WARNINGS AND PRECAUTIONS

- Elderly, cachectic, and debilitated patients and patients with chronic pulmonary disease: Monitor closely because of increased risk of respiratory depression. (5.4, 5.5)
- Interaction with CNS depressants: Consider dose reduction of one or both drugs because of additive effects. (5.6, 7.2)
- Hypotensive effect: Monitor during dose initiation and titration (5.7)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression and avoid use of KADIAN in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.8)

ADVERSE REACTIONS

Most common adverse reactions (>10%): constipation, nausea, and somnolence. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Actavis Kadian LLC at 1-888-496-3082 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Mixed agonist/antagonist opioid analgesics: Avoid use with KADIAN because they may reduce analgesic effect of KADIAN or precipitate withdrawal symptoms. (5.11, 7.3)
- Muscle relaxants: Avoid use with KADIAN because of increased risk of respiratory depression. (7.4)
- Monoamine oxidase inhibitors (MAOIs): Avoid KADIAN in patients taking MAOIs or within 14 days of stopping such treatment. (7.5)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: Morphine has been detected in human milk. Closely monitor infants of nursing women receiving KADIAN. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2012

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

KADIAN contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit [see Warnings and Precautions (5.1)]. Assess each patient's risk for opioid abuse or addiction prior to prescribing KADIAN. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving KADIAN for signs of misuse, abuse, and addiction during treatment [see Drug Abuse and Dependence (9)].

Life-threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of KADIAN, even when the drug has been used as recommended and not misused or abused [see Warnings and Precautions (5.2)]. Proper dosing and titration are essential and KADIAN should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor 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 and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine.

Accidental Exposure

Accidental consumption of KADIAN, especially in children, can result in a fatal overdose of morphine [see Warnings and Precautions (5.3)].

1 INDICATIONS & USAGE

KADIAN is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Use

KADIAN is not for use:

- As an as-needed (prn) analgesic
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.
  KADIAN 100 mg, 130 mg, 150 mg, and 200 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid-tolerant are those taking at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

2 DOSAGE & ADMINISTRATION

2.1 Initial Dosing

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with KADIAN [see Warnings and Precautions (5.2)].

Consider the following factors when selecting an initial dose of KADIAN:

- Total daily dose, potency, and any prior opioid the patient has been taking previously;
- Reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed (Note: potency estimates may vary with the route of administration);
- Patient's degree of opioid experience and opioid tolerance;
- General condition and medical status of the patient;
- Concurrent medication;
- Type and severity of the patient's pain.
  KADIAN is administered at a frequency of either once daily (every 24 hours) or twice daily (every 12 hours).
  Use of KADIAN as the First Opioid Analgesic
  There has been no evaluation of KADIAN as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient to adequate analgesia using an extended-release morphine, begin treatment using an immediate-release morphine formulation and then convert patients to KADIAN as described below.
  Conversion from Other Oral Morphine Formulations to KADIAN
  Patients receiving other oral morphine formulations may be converted to KADIAN by administering one-half of the patient's total daily oral morphine dose as KADIAN twice daily or by administering the total daily oral morphine dose as KADIAN once daily. There are no data to support the efficacy or safety of prescribing KADIAN more frequently than every 12 hours.
  KADIAN is not bioequivalent to other extended-release morphine preparations. Conversion from KADIAN to the same total daily dose of another extended-release morphine product may lead to either excessive sedation at peak or inadequate analgesia at trough. Therefore, monitor patients

closely when initiating KADIAN therapy and adjust the dosage of KADIAN as needed.

Conversion from Parenteral Morphine, or Other Opioids to KADIAN

While there are useful tables of oral and parenteral equivalents, there is substantial inter-patient variation in the relative potency of different opioid drugs and formulations. As such, it is safer to underestimate a patient's 24-hour oral morphine requirement and provide rescue medication (e.g. immediate-release morphine) than to overestimate and manage an adverse reaction. Consider the following general points:

Parenteral to Oral Morphine Ratio: Between 2 mg and 6 mg of oral morphine may be required to provide analgesia equivalent to 1 mg of parenteral morphine. Typically, a dose of oral morphine that is three times the daily parenteral morphine requirement is sufficient.

Other Oral or Parenteral Opioids to Oral Morphine Sulfate: Specific recommendations are not available because of a lack of systematic evidence for these types of analgesic substitutions. Published relative potency data are available, but such ratios are approximations. In general, begin with half of the estimated daily morphine requirement as the initial dose, managing inadequate analgesia by supplementation with immediate-release morphine.

The first dose of KADIAN may be taken with the last dose of any immediate-release opioid medication due to the extended-release characteristics of the KADIAN formulation.

2.2 Titration and Maintenance of Therapy

Individually titrate KADIAN to a dose that provides adequate analgesia and minimizes adverse reactions at a frequency of either once or twice daily. Continually reevaluate patients receiving KADIAN to assess the maintenance of pain control and the relative incidence of adverse reactions. During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), periodically reassess the continued need for the use of opioid analgesics.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the KADIAN dose to decrease the level of pain. Because steady-state plasma concentrations are approximated within 24 to 36 hours, KADIAN dosage adjustments may be done every 1 to 2 days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with a small dose of an immediate-release medication. In patients experiencing inadequate analgesia with once daily dosing of KADIAN, consider a twice daily regimen.

If signs of excessive opioid-related adverse reactions are observed, the next dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.3 Discontinuation of KADIAN

When a patient no longer requires therapy with KADIAN, use a gradual downward titration, of the dose every two to four days, to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue KADIAN.

2.4 Administration of KADIAN

Instruct patients to swallow KADIAN capsules intact. The pellets in the capsules are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of morphine [see Warnings and Precautions (5.2)].

Alternatively, the contents of the KADIAN capsules (pellets) may be sprinkled over applesauce and then swallowed. This method is appropriate only for patients able to reliably swallow the applesauce without chewing. Other foods have not been tested and should not be substituted for applesauce.

Instruct the patient to:

- Sprinkle the pellets onto a small amount of applesauce and consume immediately without chewing.
- Rinse the mouth to ensure all pellets have been swallowed.
- Discard any unused portion of the KADIAN capsules after the contents have been sprinkled on applesauce.

  The contents of the KADIAN capsules (pellets) may be administered through a 16 French gastrostomy tube.
- Flush the gastrostomy tube with water to ensure that it is wet.
- Sprinkle the KADIAN Pellets into 10 mL of water.
- Use a swirling motion to pour the pellets and water into the gastrostomy tube through a funnel.
- Rinse the beaker with a further 10 mL of water and pour this into the funnel.
- Repeat rinsing until no pellets remain in the beaker.

  Do not administer KADIAN pellets through a nasogastric tube.

3 DOSAGE FORMS & STRENGTHS

KADIAN contains white to off-white or tan colored polymer coated pellets, have an outer opaque capsule with colors as identified below and are available in twelve dose strengths:

Each 10 mg capsule has a light blue opaque cap printed with “KADIAN” and a light blue opaque body printed with “10 mg”.

Each 20 mg capsule has a yellow opaque cap printed with “KADIAN” and a yellow opaque body printed with “20 mg”.

Each 30 mg capsule has a blue violet opaque cap printed with “KADIAN” and a blue violet opaque body printed with “30 mg”.

Each 40 mg capsule has a yellow opaque cap printed with “KADIAN” and a blue violet opaque body printed with “40 mg”.

Each 50 mg capsule has a blue opaque cap printed with “KADIAN” and a blue opaque body printed with

“50 mg”.

Each 60 mg capsule has a pink opaque cap printed with “KADIAN” and a pink opaque body printed with “60 mg”.

Each 70 mg capsule has a light blue opaque cap printed with “KADIAN” and a blue violet opaque body printed with “70 mg”.

Each 80 mg capsule has a light orange opaque cap printed with “KADIAN” and a light orange opaque body printed with “80 mg”.

Each 100 mg capsule has a green opaque cap printed with “KADIAN” and a green opaque body printed with “100 mg”.

Each 130 mg capsule has a light orange opaque cap printed with “KADIAN” and a light brown opaque body printed with “130 mg”.

Each 150 mg capsule has a green opaque cap printed with “KADIAN” and a light brown opaque body printed with “150 mg”.

Each 200 mg capsule has a light brown opaque cap printed with “KADIAN” and light brown opaque body printed with “200 mg”.

4 CONTRAINDICATIONS

KADIAN is contraindicated in patients with

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity (e.g., anaphylaxis) to morphine [see Adverse Reactions (6.2)]

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

KADIAN contains morphine, an opioid agonist and a Schedule II controlled substance. Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing KADIAN in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient’s risk for opioid abuse or addiction prior to prescribing KADIAN. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of KADIAN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death [see Overdosage (10)].

Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life Threatening Respiratory Depression

Respiratory depression is the primary risk of KADIAN. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a “sighing” pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status [see Overdosage (10)].

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. Closely monitor patients for respiratory depression when initiating therapy with KADIAN and following dose increases. Instruct patients against use by individuals other than the patient for whom KADIAN was prescribed and to keep KADIAN out of the reach of children, as such inappropriate use may result in fatal respiratory depression.

To reduce the risk of respiratory depression, proper dosing and titration of KADIAN are essential [see Dosage and Administration (2.1, 2.2)]. Overestimating the KADIAN dose when converting patients from another opioid product can result in fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-release opioids when used as recommended and not misused or abused.

To further reduce the risk of respiratory depression, consider the following:

- Proper dosing and titration are essential and KADIAN should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. KADIAN 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant

patients only. Ingestion of this strength of KADIAN capsules or of the pellets within the capsule may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids.

- Instruct patients to swallow KADIAN capsules intact or to sprinkle the capsule contents on applesauce and swallow without chewing. The pellets in the capsules are not to be crushed, dissolved, or chewed. The resulting morphine dose may be fatal, particularly in opioid-naïve individuals.
- KADIAN is contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression [see Contraindications (4)].

5.3 Accidental Exposure

Accidental consumption of KADIAN, especially in children, can result in a fatal overdose of morphine.

5.4 Elderly, Cachectic, and Debilitated Patients

Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance compared to younger, healthier patients. Therefore, monitor such patients closely, particularly when initiating and titrating KADIAN and when KADIAN is given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.2)].

5.5 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with KADIAN, as in these patients, even usual therapeutic doses of KADIAN may decrease respiratory drive to the point of apnea [see Warnings and Precautions (5.2)]. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.6 Interactions with CNS Depressants and Illicit Drugs

Hypotension, profound sedation, coma, or respiratory depression may result if KADIAN is used concomitantly with other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). When considering the use of KADIAN in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, consider the patient's use, if any, of alcohol or illicit drugs that cause CNS depression. If KADIAN therapy is to be initiated in a patient taking a CNS depressant, start with a lower KADIAN dose than usual and monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant [see Drug Interactions (7.2)].

5.7 Hypotensive Effect

KADIAN may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) [see Drug Interactions (7.2)]. Monitor these patients for signs of hypotension after initiating or titrating the dose of KADIAN. In patients with circulatory shock, KADIAN may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of KADIAN in patients with circulatory shock.

5.8 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking KADIAN who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with KADIAN. KADIAN may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of KADIAN in patients with impaired consciousness or coma.

5.9 Use in Patients with Gastrointestinal Conditions

KADIAN is contraindicated in patients with paralytic ileus. Avoid the use of KADIAN in patients with other GI obstruction.

The morphine in KADIAN may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms. Opioids may cause increases in the serum amylase.

5.10 Use in Patients with Convulsive or Seizure Disorders

The morphine in KADIAN may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during KADIAN therapy.

5.11 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including KADIAN. In these patients, mixed agonists/antagonists analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing KADIAN, gradually taper the dose [see Dosage and Administration (2.3)]. Do not

abruptly discontinue KADIAN.

5.12 Driving and Operating Machinery

KADIAN may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of KADIAN and know how they will react to the medication.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Respiratory Depression [see Warnings and Precautions (5.2)]
- Chronic Pulmonary Disease [see Warnings and Precautions (5.5)]
- Head Injuries and Increased Intracranial Pressure [see Warnings and Precautions (5.8)]
- Interactions with Other CNS Depressants [see Warnings and Precautions (5.6)]
- Hypotensive Effect [see Warnings and Precautions (5.7)]
- Gastrointestinal Effects[see Warnings and Precautions (5.9)]
- Seizures [see Warnings and Precautions (5.10)]

In the randomized study, the most common adverse reactions with KADIAN therapy were drowsiness, constipation, nausea, dizziness, and anxiety. The most common adverse reactions leading to study discontinuation were nausea, constipation (may be severe), vomiting, fatigue, dizziness, pruritus, and somnolence.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical trial patients with chronic cancer pain (n=227) **(AE by Body System as seen in 2% or more of patients)**	Percentage %
CENTRAL NERVOUS SYSTEM	**28**
Drowsiness	9
Dizziness	6
Anxiety	5
Confusion	4
Dry Mouth	3
Tremor	2
GASTROINTESTINAL	**26**
Constipation	9
Nausea	7
Diarrhea	3
Anorexia	3
Abdominal pain	3
Vomiting	2
BODY AS A WHOLE	**16**
Pain	3
Disease progression	3
Chest pain	2
Diaphoresis	2
Fever	2
Asthenia	2
Accidental Injury	2
RESPIRATORY	**3**
Dyspnea	3
SKIN & APPENDAGES	**3**
Rash	3
METABOLIC & NUTRITIONAL	**3**
Peripheral edema	3
HEMIC & LYMPHATIC	**4**
Anemia	2
Leukopenia	2

In 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 (9%), nausea (7%), dizziness (6%), and anxiety (6%). Other less common side effects expected from KADIAN or seen in less than 2% of patients in the clinical trials were:

- Body as a Whole: Headache, chills, flu syndrome, back pain, malaise, withdrawal syndrome
- Cardiovascular: Tachycardia, atrial fibrillation, hypotension, hypertension, pallor, facial flushing, palpitations, bradycardia, syncope
- Central Nervous System: Confusion, anxiety, abnormal thinking, abnormal dreams, lethargy, depression, loss of concentration, insomnia, amnesia, paresthesia, agitation, vertigo, foot drop, ataxia, hypesthesia, slurred speech, hallucinations, vasodilation, euphoria, apathy, seizures,

myoclonus
- Endocrine:Hyponatremia due to inappropriate ADH secretion, gynecomastia
- Gastrointestinal: Dysphagia, dyspepsia, stomach atony disorder, gastro-esophageal reflux, delayed gastric emptying, biliary colic
- Hemic and Lymphatic: Thrombocytopenia
- Metabolic and Nutritional:Hyponatremia, edema
- Musculoskeletal:Back pain, bone pain, arthralgia
- Respiratory:Hiccup, rhinitis, atelectasis, asthma, hypoxia, respiratory insufficiency, voice alteration, depressed cough reflex, non-cardiogenic pulmonary edema
- Skin and Appendages: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

Four-Week Open-Label Safety Study

In the open-label, 4-week safety study, 1418 patients' ages 18 to 85 with chronic, non-malignant pain (e.g., back pain, osteoarthritis, neuropathic pain) were enrolled. The most common adverse events reported at least once during therapy were constipation (12%), nausea (9%), and somnolence (3%). Other less common side effects occurring in less than 3% of patients were vomiting, pruritus, dizziness, sedation, dry mouth, headache, fatigue, and rash.

6.2 Post-marketing Experience

Anaphylaxis has been reported with ingredients contained in KADIAN. Advise patients how to recognize such a reaction and when to seek medical attention.

7 DRUG INTERACTIONS

7.1 Alcohol

Concomitant use of alcohol with KADIAN can result in an increase of morphine plasma levels and potentially fatal overdose of morphine. [see Clinical Pharmacology (12.3)].

7.2 CNS Depressants

Concurrent use of KADIAN and other central nervous system (CNS) depressants (e.g. sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, and profound sedation or coma. Monitor patients receiving CNS depressants and KADIAN for signs of respiratory depression and hypotension. When such combined therapy is contemplated, reduce the initial dose of one or both agents.

7.3 Mixed Agonist/Antagonist Opioid Analgesics

Mixed agonist/antagonist analgesics may reduce the analgesic effect of KADIAN and/or may precipitate withdrawal symptoms in these patients. Avoid the use of agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol) in patients receiving KADIAN.

7.4 Muscle Relaxants

Opioids may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and KADIAN for signs of respiratory depression that may be greater than otherwise expected.

7.5 Monoamine Oxidase Inhibitors (MAOIs)

The effects of morphine may be potentiated by MAOIs. Monitor patients on concurrent therapy with an MAOI and KADIAN for increased respiratory and central nervous system depression. KADIAN should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

7.6 Cimetidine

Cimetidine can potentiate morphine-induced respiratory depression. There is a report of confusion and severe respiratory depression when a patient undergoing hemodialysis was concurrently administered morphine and cimetidine. Monitor patients for respiratory depression when KADIAN and cimetidine are used concurrently.

7.7 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 enlarged prostates.

7.8 Anticholinergics

Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when KADIAN is used concurrently with anticholinergic drugs.

7.9 P-Glycoprotein (PGP) Inhibitors

PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine by about two-fold. Monitor patients for signs of respiratory and central nervous system depression when PGP inhibitors are used concurrently with KADIAN.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects (Pregnancy Category C)

No formal studies to assess the teratogenic effects of morphine in animals have been conducted. It is also not known whether morphine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Morphine should be given to a pregnant woman only if clearly needed.

In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. In rats treated with subcutaneous infusions of morphine during the period of organogenesis, no teratogenicity was observed. No maternal toxicity was observed in this study; however, increased mortality and growth retardation were seen in the offspring. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.

Nonteratogenic Effects

Infants born to mothers who have taken opioids chronically may exhibit neonatal withdrawal syndrome [see Use in Specific Populations (8.6)], reversible reduction in brain volume, small size, decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been conducted. Published literature has reported that exposure to morphine during pregnancy in animals is associated with reduction in growth and a host of behavioral abnormalities in the offspring. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. Decreased litter size and viability were observed in the offspring of male rats administered morphine (25 mg/kg, IP) for 1 day prior to mating. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine persisting into adulthood.

8.2 Labor and Delivery

KADIAN is not recommended for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor.

Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. Have a specific opioid antagonist, such as naloxone or nalmefene, available for reversal of opioid-induced respiratory depression in the neonate.

8.3 Nursing Mothers

Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. The amount of morphine received by the infant varies depending on the maternal plasma concentration, the amount of milk ingested by the infant, and the extent of first pass metabolism.

Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine 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.

8.4 Pediatric Use

The safety and efficacy of KADIAN in patients less than 18 years have not been established.

8.5 Geriatric Use

Clinical studies of KADIAN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Neonatal Opioid Withdrawal Syndrome

Chronic maternal use of morphine during pregnancy can affect the fetus with subsequent withdrawal signs. Neonatal 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 withdrawal syndrome vary based on the drug used, duration of use, the dose of last maternal use, and rate of elimination drug by the newborn. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

KADIAN contains morphine, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. KADIAN can be abused and is subject to misuse, addiction, and criminal diversion [see Warnings and Precautions (5.1)].

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to, the following examples: the use of a prescription or over-the counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug seeking” behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

KADIAN, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests as required by state law, is strongly advised.

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

Risks Specific to Abuse of KADIAN

KADIAN is for oral use only. Abuse of KADIAN poses a risk of overdose and death. This risk is increased with concurrent abuse of KADIAN with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved KADIAN enhances drug release and increases the risk of over dose and death.

Due to the presence of talc as one of the excipients in KADIAN, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a 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, buprenorphine, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage KADIAN should not be abruptly discontinued [see Dosage and Administration (2.3)]. If KADIAN is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms [see Use in Specific Populations (8.2, 8.6)].

10 OVERDOSAGE

Clinical Presentation

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 of Overdose

In cases of overdose, priorities are the re-establishment of a patent airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of cardiac and/or pulmonary failure as needed. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. 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 patients 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.

Because the duration of reversal would be expected to be less than the duration of action of morphine in KADIAN, carefully monitor the patient until spontaneous respiration is reliably re-established. KADIAN will continue to release morphine adding to the morphine load for up to 24 hours after administration, necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be given as directed in the product's prescribing information.

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. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

KADIAN (morphine sulfate) Extended-Release capsules are for oral use and contain pellets of morphine sulfate. Morphine sulfate is an agonist at the mu-opioid receptor.

Each KADIAN extended-release capsule contains either 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, or 200 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: hypromellose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, corn starch, and sucrose.

The capsule shells contain gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and black ink, D&C red #28, FD&C blue #1 (10 mg), D&C yellow #10 (20 mg), FD&C red #3, FD&C blue #1 (30 mg), D&C yellow #10, FD&C blue #1, FD&C red #3 (40 mg), D&C red #28, FD&C red #40, FD&C blue #1 (50 mg), D&C red #28, FD&C red #40, FD&C blue #1 (60 mg), D&C red #28, FD&C blue #1, FD&C red #3 (70 mg), FD&C blue #1, FD&C red #40, FD&C yellow #6 (80 mg), D&C yellow #10, FD&C blue #1 (100 mg), FD&C red #40, FD&C blue #1, FD&C yellow #6, black iron oxide, red iron oxide, yellow iron oxide (130 mg), FD&C blue #1, D&C yellow #10, black iron oxide, red iron oxide, yellow iron oxide (150 mg), black iron oxide, yellow iron oxide, red iron oxide (200 mg). The imprint ink contains black iron oxide, potassium hydroxide, propylene glycol, and shellac.

The chemical name of morphine sulfate is 7,8-didehydro-4,5 (- epoxy-17-methyl-morphinan-3,6 (- diol sulfate (2:1) (salt) pentahydrate. The empirical formula is $(C_{17}H_{19}NO_3)_2 \bullet H_2SO_4 \bullet 5H_2O$ and its molecular weight is 758.85.

Morphine sulfate is an odorless, white, crystalline powder with a bitter taste. It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol: water partition coefficient of morphine is 1.42 at physiologic pH and the pK_b is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4). Its structural formula is:

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Morphine sulfate, an opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine sulfate include analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release, physical dependence, and alterations of the endocrine and autonomic nervous systems.

Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors located throughout the body. Morphine acts as a full agonist, binding with and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

Effects on the Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation. Specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects. Morphine produces respiratory depression by direct action on brainstem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brainstem respiratory centers to increases in carbon dioxide tension, and to electrical stimulation. Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Morphine causes miosis, even in total darkness, and little tolerance develops to this effect. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia in the setting of morphine overdose.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Effects on the Cardiovascular System

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

Effects on the Endocrine System

Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

12.2 Pharmacodynamics

Plasma Level-Analgesia Relationships

While plasma morphine-efficacy relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. The effective dose in opioid-tolerant patients may be 10 to 50 times as great (or greater) than the appropriate dose for opioid-naïve individuals. Dosages of morphine should be chosen and must be titrated on the basis of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

CNS Depressant/Alcohol Interaction

Additive pharmacodynamic effects may be expected when KADIAN is used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

12.3 Pharmacokinetics

Absorption

KADIAN capsules contain polymer coated extended-release pellets of morphine sulfate that release morphine significantly more slowly than oral morphine solution. Following the administration of oral morphine solution, approximately 50% of the morphine absorbed reaches the systemic circulation within 30 minutes compared to 8 hours with an equal amount of KADIAN. Because of pre-systemic elimination, only about 20 to 40% of the administered dose reaches the systemic circulation.

Both dose-normalized C_{max} and dose-normalized $AUC_{0\text{-}48hr}$ values of morphine after a single dose administration of KADIAN in healthy volunteers are less than those for morphine oral solution or an extended-release tablet formulation (Table 1).

When KADIAN was given twice daily to 24 patients with chronic pain due to malignancy, steady state was achieved in about two days. At steady state, KADIAN has a significantly lower C_{max} and a higher

C_{min} than equivalent doses of oral morphine solution given every 4 hrs and an extended-release tablet given twice daily. When given once daily to 24 patients with malignancy, KADIAN had a similar C_{max} and higher C_{min} at steady state when compared to an extended-release morphine tablets, given twice daily at an equivalent total daily dosage (see Table 1).

The single-dose pharmacokinetics of KADIAN are linear over the dosage range of 30 to 100 mg.

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

Regimen/Dosage Form	AUC#,+ (ng.h/mL)	C_{max}+ (ng/mL)	T_{max} (h)	C_{min}+ (ng/mL)	Fluctuation*
Single Dose (n=24)					
KADIAN Capsule	271.0 (19.4)	15.6 (24.4)	8.6 (41.1)	na^	na
Extended-Release Tablet	304.3 (19.1)	30.5 (32.1)	2.5 (52.6)	na	na
Morphine Solution	362.4 (42.6)	64.4 (38.2)	0.9 (55.8)	na	na
Multiple Dose (n=24)					
KADIAN Capsule Once Daily	500.9 (38.6)	37.3 (37.7)	10.3 (32.2)	9.9 (52.3)	3.0 (45.5)
Extended-Release Tablet Twice Daily	457.3 (40.2)	36.9 (42.0)	4.4 (53.0)	7.6 (60.3)	4.1 (51.5)

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

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

Distribution

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. The volume of distribution of morphine is approximately 3 to 4 L/kg. Morphine is 30 to 35% reversibly bound to plasma proteins. Although the primary site of action of morphine is in the CNS, only small quantities pass the blood-brain barrier. Morphine also crosses the placental membranes [see Use in Special Populations (8.1)] and has been found in breast milk [see Use in Specific Populations (8.3)].

Metabolism

Major pathways of morphine metabolism include glucuronidation in the liver to produce metabolites including morphine-3-glucuronide, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5 to 15%) and sulfation in the liver to produce morphine-3-etheral sulfate. A small fraction (less than 5%) of morphine is demethylated. M3G has no significant contribution to the analgesic activity. Although M6G does not readily cross the blood-brain barrier, it has been shown to have opioid agonist and analgesic activity in humans.

Studies in healthy subjects and cancer patients have shown that the glucuronide metabolite to morphine mean molar ratios (based on AUC) are similar after both single doses and at steady state for KADIAN, 12-hour extended-release morphine sulfate tablets and morphine sulfate solution.

Excretion

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

The mean adult plasma clearance of morphine is about 20 to 30 mL/minute/kg. The effective terminal half-life of morphine after IV administration is reported to be approximately 2 hours. The terminal elimination half-life of morphine following a single dose of KADIAN administration is approximately 11 to 13 hours.

Special Populations

Geriatric Patients: The pharmacokinetics of KADIAN have not been investigated in elderly patients (>65 years) although such patients were included in the clinical studies.

Pediatric Patients: The pharmacokinetics of KADIAN have not been evaluated in a pediatric population.

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

Race: Chinese subjects given intravenous morphine in one study had a higher clearance when compared to Caucasian subjects (1852 $\pm$ 116 mL/min versus 1495 $\pm$ 80 mL/min).

Hepatic Impairment: The pharmacokinetics of morphine were found to be significantly altered in individuals with alcoholic cirrhosis. The clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these patients indicating a decrease in metabolic activity. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted.

Renal Impairment: The pharmacokinetics of morphine are altered in patients with renal failure. The AUC is increased and clearance is decreased. Metabolites, M3G and M6G accumulate several fold in patients with renal failure compared to healthy subjects. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.

Mutagenesis: No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic *in vitro* increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the *in vivo* mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the *in vivo* clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the above positive findings, *in vitro* studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in *Drosophila*.

Impairment of Fertility: No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted. Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites were seen. Studies from the literature have also reported changes in hormonal levels (i.e. testosterone, luteinizing hormone, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.

16 HOW SUPPLIEDSTORAGE AND HANDLING

KADIAN capsules contain white to off-white or tan colored polymer coated extended-release pellets of morphine sulfate and are available in twelve dose strengths.

	KADIAN 10 mg	**KADIAN 20 mg**	**KADIAN 30 mg**	**KADIAN 40 mg**
Capsule Description	size 4, light blue opaque cap printed with “KADIAN” and light blue opaque body printed with “10 mg”.	size 4, yellow opaque cap printed with “KADIAN” and yellow opaque body printed with “20 mg”.	size 4, blue violet opaque cap printed with “KADIAN” and blue violet opaque body printed with “30 mg”.	size 2, yellow opaque cap printed with “KADIAN” and blue violet opaque body printed with “40 mg”.
Bottle Size	100	100	100	100
NDC #	NDC 46987-410-11	NDC 46987-322-11	NDC 46987-325-11	NDC 46987-327-11

	KADIAN 50 mg	**KADIAN 60 mg**	**KADIAN 70 mg**	**KADIAN 80 mg**
Capsule Description	size 2, blue opaque cap printed with “KADIAN” and blue opaque body printed with “50 mg”.	size 1, pink opaque cap printed with “KADIAN” and pink opaque body printed with “60 mg”.	size 1EL, light blue opaque cap printed with “KADIAN” and blue violet opaque body printed with “70 mg”.	size 0, light orange opaque cap printed with “KADIAN” and light orange opaque body printed with “80 mg”.
Bottle Size	100	100	100	100
NDC #	NDC 46987-323-11	NDC 46987-326-11	NDC 46987-328-11	NDC 46987-412-11

	KADIAN 100 mg	**KADIAN 130 mg**	**KADIAN 150 mg**	**KADIAN 200 mg**
Capsule Description	size 0, green opaque cap printed with “KADIAN” and green opaque body printed with “100 mg”.	size 1, light orange opaque cap printed with “KADIAN” and light brown opaque body printed with “130 mg”.	size 1EL, green opaque cap printed with “KADIAN” and light brown opaque body printed with “150 mg”.	size 0, light brown opaque cap printed with “KADIAN” and light brown opaque body printed with “200 mg”.
Bottle Size	100	100	100	100
NDC #	NDC 46987-324-11	NDC 46987-329-11	NDC 46987-330-11	NDC 46987-377-11

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Protect from light and moisture. Dispense in a sealed tamper-evident, childproof, light-resistant container.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Abuse Potential

Inform patients that KADIAN contains morphine, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share KADIAN with others and to take steps to protect KADIAN from theft or misuse.

Life-threatening Respiratory Depression

Discuss the risk of respiratory depression with patients, explaining that the risk is greatest when starting KADIAN or when the dose is increased. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Accidental Exposure

Instruct patients to take steps to store KADIAN securely. Accidental exposure, especially in children, may result in serious harm or death. Advise patients to dispose of unused KADIAN by flushing the capsules down the toilet.

Risks from Concomitant Use of Alcohol and other CNS Depressants

Inform patients that the concomitant use of alcohol with KADIAN can increase the risk of life-threatening respiratory depression.

Inform patients that potentially serious additive effects may occur if KADIAN is used with other CNS depressants, and not to use such drugs unless supervised by a health care provider.

Important Administration Instructions

Instruct patients how to properly take KADIAN, including the following:

- Swallowing KADIAN capsules whole or sprinkling the capsule contents on applesauce and then swallowing without chewing
- Not crushing, chewing, or dissolving the pellets in the capsules
- Using KADIAN exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Not discontinuing KADIAN without first discussing the need for a tapering regimen with the prescriber

Hypotension

Inform patients that KADIAN may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

Driving or Operating Heavy Machinery

Inform patients that KADIAN may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Anaphylaxis

Inform patients that anaphylaxis has been reported with KADIAN. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy

Advise female patients that KADIAN can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Distributed by: Actavis Kadian LLC, 60 Columbia Rd., Bldg. B, Morristown, NJ 07960 USA

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40-9166

MEDICATION GUIDE

KADIAN® (key-dee-uhn)

(morphine sulfate extended-release) Capsules, CII

KADIAN® is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to treat moderate to severe around-the-clock pain.

Important information about KADIAN®:

- Get emergency help right away if you take too much KADIAN® (overdose). KADIAN® overdose can cause life threatening breathing problems that can lead to death.
- Never give anyone else your KADIAN®. They could die from taking it. Store KADIAN® away from children and in a safe place to prevent stealing or abuse. Selling or giving away KADIAN® is against the law.

Do not take KADIAN® if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking KADIAN®, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** KADIAN® may harm your unborn baby.
- **breastfeeding**. KADIAN® passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements.

When taking KADIAN®:

- Do not change your dose. Take KADIAN® exactly as prescribed by your healthcare provider.

- Take your prescribed dose at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take KADIAN® as soon as possible and then take your next dose 12 or 24 hours later as directed by your healthcare provider. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule.
- Swallow KADIAN® whole. Do not cut, break, chew, crush, dissolve, or inject KADIAN®.
- If you cannot swallow KADIAN® capsules, see the detailed Instructions for Use.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking KADIAN® without talking to your healthcare provider.**
- After you stop taking KADIAN®, flush any unused capsules down the toilet.

While taking KADIAN® Do Not:

- Drive or operate heavy machinery, until you know how KADIAN® affects you. KADIAN® can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

The possible side effects of KADIAN® are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.
  Get emergency medical help if you have:
- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, or you are feeling faint.
  These are not all the possible side effects of KADIAN®. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**
  KADIAN® is a registered trademark of Actavis Elizabeth LLC.
  Distributed by: Actavis Kadian LLC, 60 Columbia Rd., Bldg. B, Morristown, NJ 07960 USA, www.KADIAN.com or call 1-888-496-3082
  This Medication Guide has been approved by the U.S. Food and Drug Administration. Issue: July 2012

INSTRUCTIONS FOR USE

KADIAN® (key-dee-uhn)

(morphine sulfate extended-release) Capsules, CII

If you cannot swallow KADIAN® capsules, tell your healthcare provider. There may be another way to take KADIAN® that may be right for you. If your doctor tells you that you can take KADIAN® using this other way, follow these steps:

KADIAN® can be opened and the pellets inside the capsule can be sprinkled over apple sauce, as follows:

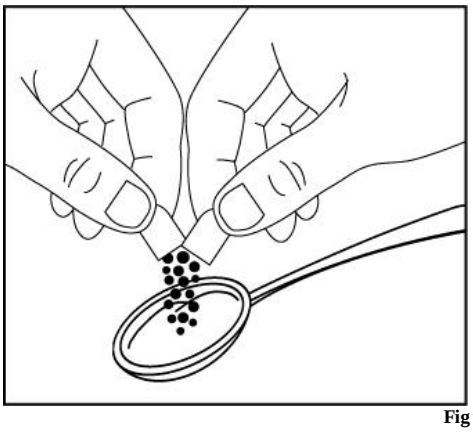

Figure 1

- Open the KADIAN® capsule and sprinkle the pellets over approximately one tablespoon of apple sauce (Figure 1).

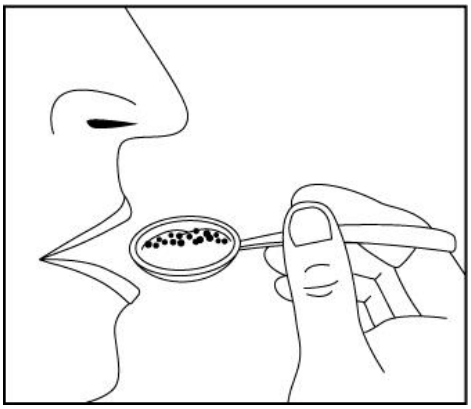

Figure 2

- Swallow all of the apple sauce and pellets right away. Do not save any of the apple sauce and pellets for another dose (Figure 2).

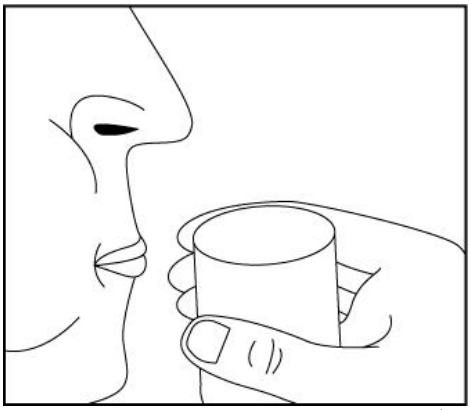

Figure 3

- Rinse your mouth to make sure you have swallowed all of the pellets. Do not chew the pellets (Figure 3).

Figure 4

- Flush the empty capsule down the toilet right away (Figure 4).

You should not receive KADIAN® through a nasogastric tube.

KADIAN

morphine sulfate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63629-4694(NDC:46987-325)
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MORPHINE SULFATE (UNII: X3P646A2J0) (MORPHINE - UNII:76I7G6D29C)	MORPHINE SULFATE	30 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1) (UNII: 74G4R6TH13)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
DIETHYL PHTHALATE (UNII: UF064M00AF)	
TALC (UNII: 7SEV7J4R1U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
GELATIN (UNII: 2G86QN327L)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
SHELLAC (UNII: 46N107B71O)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	BLUE (VIOLET)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	Kadian;30;mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-4694-1	60 in 1 BOTTLE		
2	NDC:63629-4694-2	30 in 1 BOTTLE		

Marketing Information

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

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-4694) , RELABEL(63629-4694)