FILE COPY

October 14, 2010

UPS OVERNIGHT COURIER

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA # 20-616 KADIAN® (morphine sulfate extended-release) Capsules, 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg

Dear Sir/Madam:

Actavis Elizabeth LLC is hereby submitting, in duplicate, the following promotional material(s), for KADIAN® (morphine sulfate extended-release) Capsules:

KADIAN Detail Aid
KADI1005

If you have any questions relating to this submission, please do not hesitate to contact the undersigned at (908) 659-3017, fax number (908) 659-2250, or via secure email to RegulatoryAffairsUS@actavis.com.

Sincerely,

ACTAVIS ELIZABETH LLC

Charlene Salmorin
Director, Labeling
Regulatory Affairs

CS/cch
Enclosures

Actavis Elizabeth LLC
Actavis Mid Atlantic LLC
200 Elmora Avenue
Elizabeth, NJ 07207
t 908 527 9100
f 908 659 2250
www.actavis.com

Form Approved: OMB No. 0910-0001, Expiration Date: May 31, 2011; see OMB Statement on Page 3.

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. DATE SUBMITTED: 10/14/2010

2. LABEL REVIEW NO. (Biologics):

3. NDA/ANDA/AADA OR BLA/PLA/PMA
Number: 20-616
Single product ☒ Multiple products ☐
For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice, and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.

NOTE: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)

4. PROPRIETARY NAME	5. ESTABLISHED NAME
KADIAN	Morphine Sulfate Extended-Release Capsules Prod. Code No. N/A
6. PACKAGE INSERT DATE and ID NO. (Latest final printed labeling) Rev. February 2010 Part# 40-9101	7. MANUFACTURER NAME: License No. (Biologics)

FDA/CBER USE ONLY

REVIEWED BY	DATE	RETURNED BY	DATE

8. **ADVERTISEMENT / PROMOTIONAL LABELING MATERIALS**

Please check only one: ☒ Professional ☐ Consumer

Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS:
PSA	10/15/10	KADIAN Detail Aid KADI1005	N/A	
				Add Continuation Page

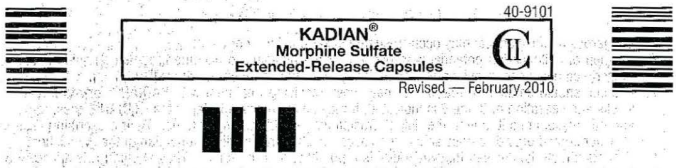
9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Charlene Salmorin
Director, Labeling, Regulatory Affairs

10. SIGNATURE OF RESPONSIBLE OFFICIAL
Charlene Salmorin

11. APPLICANT'S RETURN ADDRESS
200 Elmora Avenue
Elizabeth, NJ 07207 USA

12. RESPONSIBLE OFFICIAL'S
a. PHONE NO.
(908) 659-3017
b. FAX NO.
(908) 659-2250

13. FOR CBER PRODUCTS ONLY: *(Check one)*
☐ Part I/Draft ☐ Part II/Final



40-9101

KADIAN®
Morphine Sulfate
Extended-Release Capsules

C II

Revised — February 2010

KADIAN® (morphine sulfate extended-release) Capsules

Interactions with other CNS Depressants

KADIAN® should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result.

Gastrointestinal Obstruction

KADIAN® should not be given to patients with gastrointestinal obstruction, particularly paralytic ileus, as there is a risk of the product remaining in the stomach for an extended period and the subsequent release of a bolus of morphine when normal gut motility is restored. As with other solid morphine formulations diarrhea may reduce morphine absorption.

Other

Although extremely rare, cases of anaphylaxis have been reported.

PRECAUTIONS

General

CARLA HEDRICK
908-659-2527
ACTAVIS ELIZABETH LLC
200 ELMORA AVENUE
ELIZABETH NJ 072021106

0.0 LBS LTR

1 OF 1

SHIP TO:
FDA, CDER, DDMAC
5901-B AMMENDALE ROAD
BELTSVILLE MD 20705-1266

MD 207 9-59

UPS NEXT DAY AIR **1**

TRACKING #: 1Z 062 077 01 9013 3700

BILLING: P/P

Reference#1: 20-616 Detail Aid

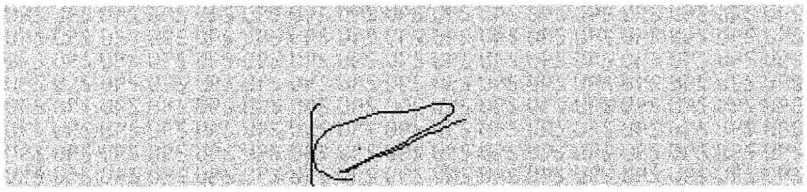
UIS 12.8.10. WXPIE60 06.0A 07/2010

Proof of Delivery

Dear Customer,

This notice serves as proof of delivery for the shipment listed below.

Tracking Number:	1Z0620770190133700
Reference Number(s):	20-616 DETAIL AID
Service:	NEXT DAY AIR
Shipped/Billed On:	10/14/2010
Delivered On:	10/15/2010 9:04 A.M.
Delivered To:	5901B AMMENDALE RD BELTSVILLE, MD, US 20705
Signed By:	WADE



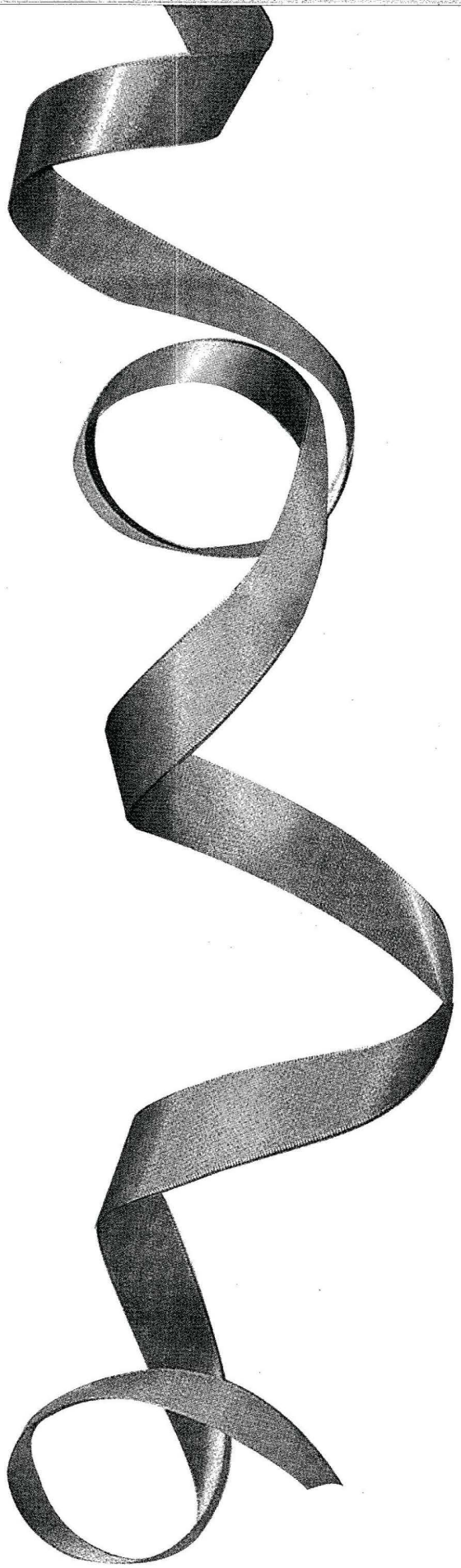
Location:	RECEIVER

Thank you for giving us this opportunity to serve you.

Sincerely,

UPS

Tracking results provided by UPS: 10/19/2010 11:34 A.M. ET



KADIAN®

Morphine Sulfate Extended-Release Capsules

10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg

Please see Boxed WARNING on page 2, Important Safety Information on pages 2-3, and accompanying Full Prescribing Information.

KADIAN®
Morphine Sulfate Extended-Release Capsules

KADIAN® 10 mg Capsules	KADIAN® 60 mg Capsules
KADIAN® 20 mg Capsules	KADIAN® 80 mg Capsules
KADIAN® 30 mg Capsules	KADIAN® 100 mg Capsules
KADIAN® 50 mg Capsules	KADIAN® 200 mg Capsules

℞ only

WARNING:

KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

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

KADIAN® 100 mg and 200 mg Capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids.

KADIAN® CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLE SAUCE. THE PELLETS IN THE CAPSULES ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

Important Safety Information

- KADIAN® is contraindicated in patients with a known hypersensitivity to morphine, morphine salts or any of the capsule components, or in any situation where opioids are contraindicated. This includes in patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute or severe bronchial asthma or hypercarbia.

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

  Care should be taken in the prescribing of the 100 mg and 200 mg capsule strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

- KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

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

  KADIAN® should be used with extreme caution in patients with chronic obstructive pulmonary disease or corpulmonale, and in patients having a substantially decreased respiratory reserve (e.g. severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

- 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 intracraniallesions, or a pre-existing increase in intracranial pressure. KADIAN® produces effects which may obscure neurologic signs of further increases in pressure in patients with head injuries. Morphine should only be administered under such circumstances when considered essential and then with extreme care.

Please see Boxed WARNING and Important Safety Information on this spread, and accompanying Full Prescribing Information.

- KADIAN® may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has already been compromised by a reduced blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics. (see **PRECAUTIONS - Drug Interactions section of Full Prescribing Information.**) KADIAN® may produce orthostatic hypotension and syncope in ambulatory patients.

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

- KADIAN® should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result.
- KADIAN® should not be given to patients with gastrointestinal obstruction, particularly paralytic ileus, as there is a risk of the product remaining in the stomach for an extended period and the subsequent release of a bolus of morphine when normal gut motility is restored. As with other solid morphine formulations diarrhea may reduce morphine absorption.
- Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.
- The administration of KADIAN® may obscure the diagnosis or clinical course in patients with acute abdominal conditions.
- KADIAN® may aggravate pre-existing convulsions in patients with convulsive disorders.
- Patients taking KADIAN® who are scheduled for cordotomy or other interruption of pain transmission pathways should have KADIAN® ceased 24 hours prior to the procedure and the pain controlled by parenteral short-acting opioids. In addition, the post-procedure titration of analgesics for such patients should be individualized to avoid either oversedation or withdrawal syndromes.
- KADIAN® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in the serum amylase level.
- Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.
- KADIAN® should be administered with caution, and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; patients with Addison's disease; myxedema; hypothyroidism; prostatic hypertrophy or urethral stricture.

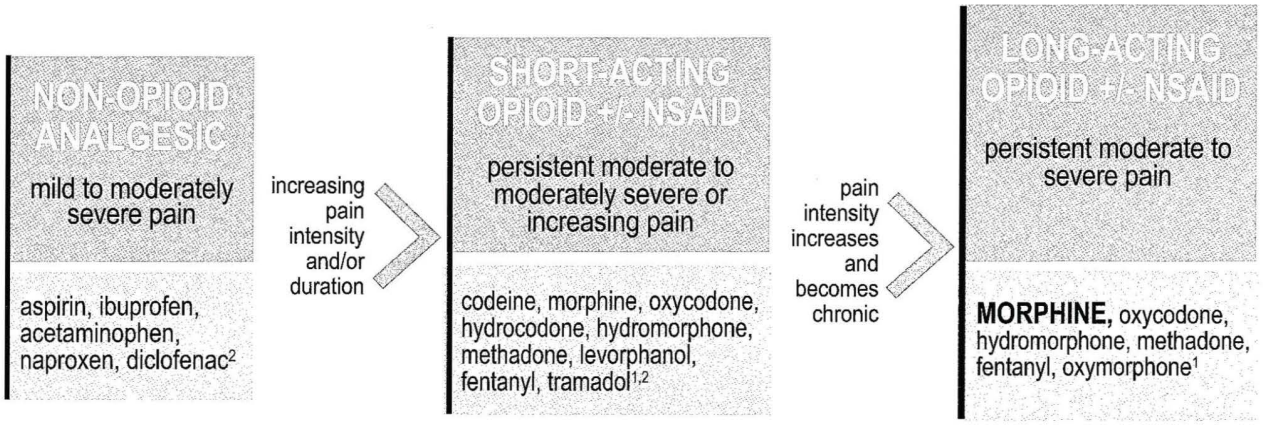
  Caution should also be exercised in the administration of KADIAN® to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens, and convulsive disorders.

  KADIAN® may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Patients must be cautioned accordingly. Patients should also be warned about the potential combined effects of KADIAN® with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol (see **Drug Interactions section of Full Prescribing Information**).
- CNS Depressants: Morphine should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma.
- Muscle Relaxants: KADIAN® may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression.
- Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as KADIAN®.
- Monoamine Oxidase Inhibitors (MAOIs): MAOIs have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion and significant depression of respiration or coma. KADIAN® should not be used in patients taking MAOIs or within 14 days of stopping such treatment.
- There is an isolated report of confusion and severe respiratory depression when a hemodialysis patient was concurrently administered morphine and cimetidine.
- Morphine can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.
- The most serious adverse events associated with KADIAN® and other opioid analgesics are respiratory depression, respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock.
- The most frequent adverse events are drowsiness, dizziness, constipation, and nausea.

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg

World Health Organization (WHO) guidelines recommend treating chronic pain with a long-acting opioid[1]

Treating pain with analgesics: an algorithm[a]



[a]*Adapted from WHO 3-step analgesic ladder.*

INDICATIONS AND USAGE

KADIAN® Capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

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

KADIAN® is not indicated for pain in the immediate post-operative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time.

KADIAN® is only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

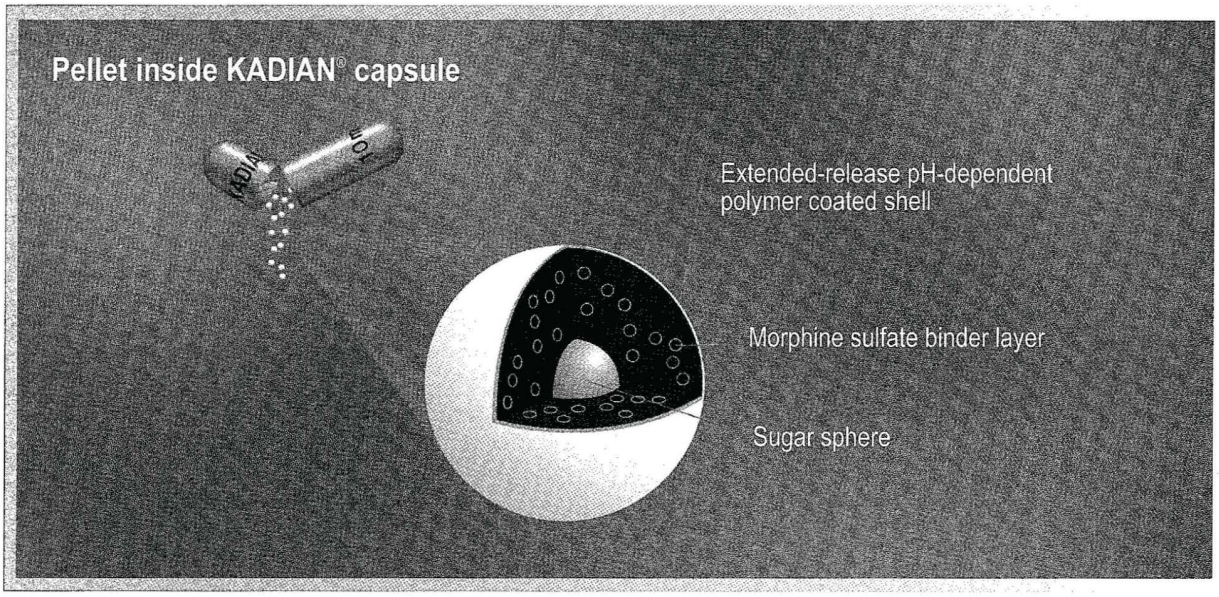
Safety considerations:

KADIAN® (morphine sulfate extended-release) Capsules contain morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Please see Boxed WARNING on page 2, Important Safety Information on pages 2-3, and accompanying Full Prescribing Information.

Reliable morphine delivery

KADIAN® utilizes polymer-coated pellet technology



Pellet and capsule are not shown at actual size

- Distinctive pellet composition releases morphine steadily into the bloodstream for up to 24 hours[3]

Absorption

Following the administration of oral morphine solution, approximately 50% of the morphine absorbed reaches the systemic circulation within 30 minutes. However, following the administration of an equal amount of KADIAN® to healthy volunteers, this occurs, on average, after 8 hours. As with most forms of oral morphine, because of pre-systemic elimination, only about 20 to 40% of the administered dose reaches the systemic circulation.

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

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

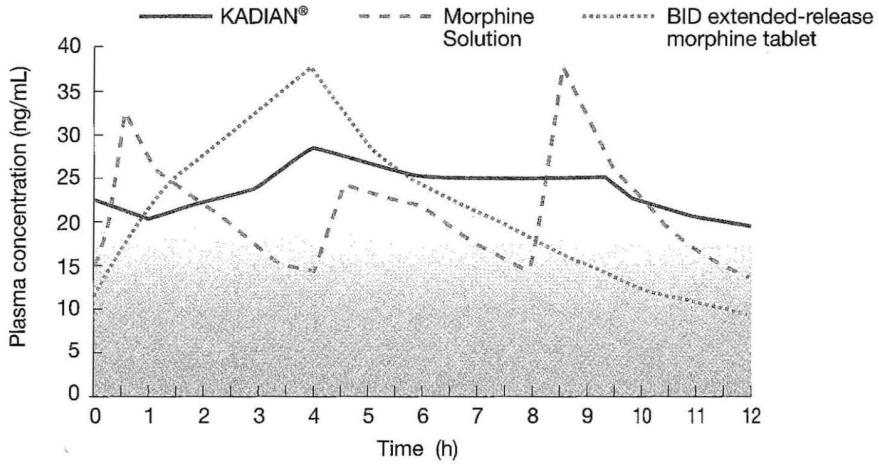
Drug-disease interactions are frequently seen in the older and more gravely ill patients, and may result in both altered absorption and reduced clearance as compared to normal volunteers.

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg•20mg•30mg•50mg•60mg•80mg•100mg•200mg

Mean Steady State Plasma Levels[3]

Graph 1 from full prescribing information (Study # MOB 1/90)

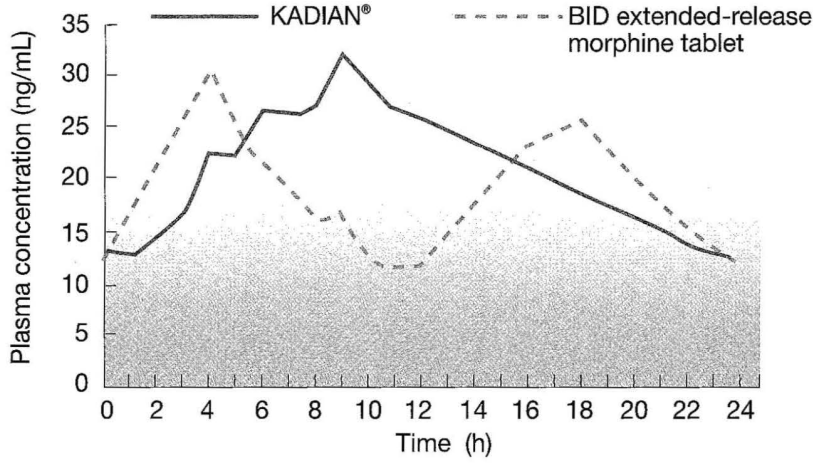
Mean steady state plasma morphine concentrations for KADIAN® (twice a day), extended-release morphine tablet (twice a day) and oral morphine solution (every 4 hours); plasma concentrations are normalized to 100 mg every 24 hours, (n=24).



Dose Normalized Mean Steady State Plasma Levels[3]

Graph 2 from full prescribing information (Study # MOR 9/92)

Dose normalized mean steady state plasma morphine concentrations for KADIAN® (once a day), and an equivalent dose of a 12-hour, extended-release morphine tablet given twice a day. Plasma concentrations are normalized to 100 mg every 24 hours, (n=24).



Please see Boxed WARNING on page 2, Important Safety Information on pages 2-3, and accompanying Full Prescribing Information.

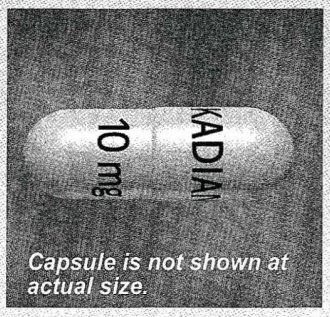
Dosing flexibility with KADIAN®

10 mg	20 mg	30 mg	50 mg	60 mg	80 mg	100 mg	200 mg

Capsules are not shown at actual size.

- 8 dosing strengths—the most of any extended-release morphine[3-5]
- Flexibility to dose q12h or q24h[3]
- Allows for titration in increments of 10 mg, with a low dose of 10 mg[3]
  - In accordance with American Pain Society guidelines about low initial dosing[2]

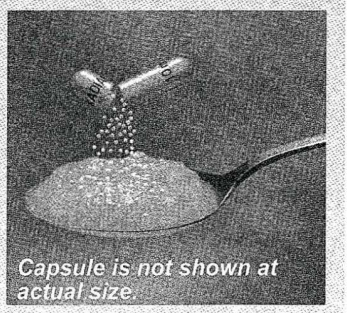
As a capsule



Capsule is not shown at actual size.

Capsule can be swallowed whole.

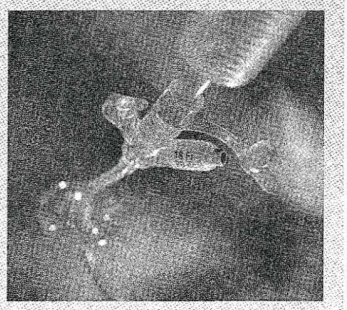
Sprinkle dosing



Capsule is not shown at actual size.

Capsule can be opened and the contents sprinkled on apple sauce for patients who have difficulty swallowing.*

G-tube dosing



Contents of capsule can be sprinkled in water and administered through a 16 French gastrostomy tube.**

*Apple sauce should be room temperature and used immediately.
**The administration of KADIAN® pellets through a nasogastric tube should not be attempted.

Safety considerations:
KADIAN® capsules are to be swallowed whole or the contents of the capsules sprinkled on apple sauce. The pellets in the capsules are not to be chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine.

Cessation of Therapy:
When the patient no longer requires therapy with KADIAN® capsules, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

KADIAN® C II
Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg

KADIAN®
Morphine Sulfate Extended-Release Capsules

CII

KADIAN® 10 mg Capsules	KADIAN® 60 mg Capsules
KADIAN® 20 mg Capsules	KADIAN® 80 mg Capsules
KADIAN® 30 mg Capsules	KADIAN® 100 mg Capsules
KADIAN® 50 mg Capsules	KADIAN® 200 mg Capsules

℞ only

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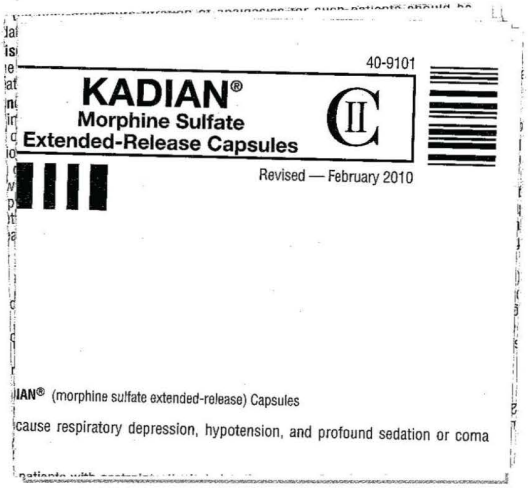
References: 1. Doyle D, Hanks GWC, MacDonald N, eds. *Oxford Textbook of Palliative Medicine*. 2nd ed. Oxford, England: Oxford University Press; 1998. **2.** American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*. 5th ed. Glenview, IL: American Pain Society; 2003. **3.** KADIAN® CII [prescribing information]. Morristown, NJ: Actavis Elizabeth LLC. 2010. **4.** Full Prescribing Information. AVINZA® CII (morphine sulfate extended-release capsules/King Pharmaceuticals Inc.). *Physicians' Desk Reference®*. 64th ed. Montvale, NJ: PDR Network, LLC; 2010:1822-1826. **5.** Full Prescribing Information. MS Contin® CII (morphine sulfate controlled-release tablets/Purdue Pharma LP). *Physicians' Desk Reference®*. 64th ed. Montvale, NJ: PDR Network, LLC; 2010:2803-2807.

For further information, please visit www.KADIAN.com or call 1-888-496-3082.

Please see accompanying Full Prescribing Information.



actavis
creating value in pharmaceuticals

KADI1005 Printed in USA

KADIAN® CII
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