actavis
creating value in pharmaceuticals

FILE COPY

March 29, 2011

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:

TMS Health Telesales Script	Material Code: KADI1111
Telemarketing Letter [Template]	Material Code: KADI1115-1
Telemarketing Letter [Template]	Material Code: KADI1115-2
Mini Conversion Guide	Material Code: KADI1107

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 of Labeling
Regulatory Affairs

CS\cg
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: 03/29/2011

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: KADIAN

5. ESTABLISHED NAME: Morphine Sulfate Extended-Release Capsules
Prod. Code No. N/A

6. PACKAGE INSERT DATE and ID NO. (Latest final printed labeling): Rev. February 2009 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:
PTL	03/28/11	TMS Health Telesales Script Material Code: KADI1111	N/A	
PLT	03/29/11	Telemarketing Letter [template] Material Code: KADI1115-1	N/A	
LT	03/29/11	Telemarketing Letter [template] Material Code: KADI1115-2	N/A	
PSA	03/29/11	Mini Conversion Guide Material Code: KADI1107	N/A	

Add Continuation Page

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Charlene Salmorin
Director of 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.
(909) 659-2250

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

TMS Health Telesales Script
Rev 3/24/11

Call Introduction for KADIAN® (morphine sulfate extended release) Capsules CII:

Gatekeeper Opening

Good morning/afternoon. This is _____. I am calling on behalf of Actavis. May I ask to whom I am speaking**? (Record the name of the Gatekeeper)**. I would like to speak with Dr _____regarding KADIAN® (morphine sulfate extended release) Capsules and recent important events regarding product availability in the long-acting opioid market. (May I speak with him/her?)

(If "YES" proceed to the PHYSICIAN SCRIPT/OPENING)

(If doctor is unavailable, follow steps below inserting where appropriate the gatekeeper and doctor's name)

1. May I hold for the possibility of reaching the doctor between patients? I will respect his/her time and be brief. I don't mind holding if that is okay with you. **(If "Yes," proceed to PHYSICIAN SCRIPT/OPENING**)

If it is not possible to hold

2. I really appreciate your help. I believe Dr._____ will be interested in information about KADIAN® and the Co-pay Assistance Card Program, offered by Actavis for KADIAN®. I would like to make an appointment to speak to him/her at a time that is convenient – perhaps early morning/around noon hour or later in the evening? **(If "Yes," schedule call back time.)** Thank you for your help. I look forward to speaking with Dr. _____ at that time.

If response is "There is no good time to speak to the doctor" or "He/she won't speak to you"

3. I understand it is difficult to reach him/her while seeing patients. May I leave my name and number and a message so he/she may contact me at his/her convenience?

If response is "He/she won't call you either"

4. Is there a nurse practitioner or physician's assistant in the office that I may be able to speak with? **(If "Yes," record name and proceed to PHYSICIAN SCRIPT/OPENING)**

If response is "No, he/she won't speak to you either" or "There is no NP or PA in this office"

5. Perhaps the nurse or Medical Assistant that works most closely with Dr._____? **(Record Nurse's name and proceed to NURSE SCRIPT/OPENING, make an appointment or leave toll-free number if necessary)**

If at any point in the conversation you are asked to "fax or mail the information"

6. We would be glad to mail the doctor information. May I confirm the doctor's mailing address? **(Verify full name, business name, mailing address.)** Thank you. When can I follow up on the information with Dr. _____? **(If requested to send info to the NP/PA, Nurse or MA they should get their name for follow up as well).**

NURSE SCRIPT/OPENING

Good morning/afternoon. My name is _____. I am calling on behalf of Actavis. Is this _____, the nurse for Dr. _____? **(Ask and record name if not already secured)** Thank you for taking my call; I will be brief.

I am trying to reach Dr._____ regarding KADIAN® (morphine sulfate extended release) Capsules. As you may know, there is an announcement on the Embeda website that all dosage forms of Embeda have been recalled to the pharmacy level. According to the website, the recall issue is unlikely to pose a safety risk to patients; however, Embeda will be unavailable for some time. To help meet the needs of your patients currently taking Embeda, your physician may decide to prescribe KADIAN® for these patients. Would you like me to mail a copy of the conversion guide to your office? (If "Yes" please take contact name and fax number and continue with script. If "No", continue with script).

Should your physician begin prescribing KADIAN®, I would like to make sure you are aware that Actavis is offering a KADIAN® Co-pay Assistance Program that may be helpful to your patients. The co-pay assistance card provides your patients with up to $50.00 towards their KADIAN® prescription co-pay or out-of-pocket costs. We would like to provide Dr. _____ with information about KADIAN® and the opportunity to discuss our patient support programs. Would it be possible to speak to Dr._____ at this time? **(If "Yes," proceed to PHYSICIAN SCRIPT/OPENING)**

If doctor is unavailable, follow same steps as with Gatekeeper).

PHYSICIAN SCRIPT/OPENING

Good morning/afternoon Dr._____. Thank you for taking my call, I will be brief. My name is _____. I am calling on behalf of Actavis regarding **KADIAN® (morphine sulfate extended release) Capsules**.

. As you may know, there is an announcement on the Embeda website that all dosage forms of Embeda have been recalled to the pharmacy level. According to the website, the recall issue is unlikely to pose a safety risk to patients; however, Embeda will be unavailable for some time. To help meet the needs of your patients currently taking Embeda, I'd like you to consider prescribing KADIAN®. Would you like me to mail a copy of the conversion guide to your office? (If "Yes" please take contact name and fax number and continue with script. If "No", continue with script).

Note: If you are cut-off at any time during the discussion of KADIAN's full indication, remind the HCP that KADIAN® is only appropriate for use in a very limited patient population who experience persistent moderate to severe pain. Also inform the HCP that following the call, you will be sending a copy of the KADIAN® PI which contains the full indication and risk information for their reference.

As you know, 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.

KADIAN® is also indicated for post-operative use only if the patient was already receiving KADIAN® prior to surgery or if the post-operative pain is expected to be moderate to severe and persist for an extended period of time.

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

KADIAN® is NOT intended for use as a PRN analgesic.

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

You also might be interested to know that that Actavis offers a **KADIAN®** CO-PAY ASSISTANCE CARD PROGRAM for your patients. The card provides your patients with up to $50.00 towards their KADIAN® prescription co-pay or out-of-pocket costs.

How do you decide which medication to prescribe for your patients with chronic pain?

Note: An HCP's response to the above question may give you an opportunity to provide additional information about KADIAN® capsules. When providing additional information or responding to questions, only communicate the most relevant/most appropriate statements from the list below that are responsive to the HCP's question. Do not read the entire list of statements unless all of the information is relevant to the discussion.

ABOUT KADIAN®

Doctor, as you may recall

- KADIAN® contains morphine as its active ingredient and has a long history of safety and efficacy when used as indicated
- KADIAN® has a well known side effect profile
- KADIAN® provides steady blood levels of morphine sulfate with few peaks and valleys
- KADIAN® is stocked in pharmacies nationwide
- KADIAN® has excellent managed care coverage with most plans at second or third tier; in fact, KADIAN® has formulary coverage for the majority of patients in the top 25 U.S. health plans (source: AIS Directory of Health Plans: 2011, Fingertip Formulary (T2 and T3) and Data on File at Actavis Elizabeth LLC).
- KADIAN® is in a preferred position on many state public aid programs
- KADIAN® has a generous co-pay assistance program. Its' $50 co-pay card significantly reduces the patient's out-of-pocket expenses
- Co-pay cards can be used 2x per month until December 31, 2010.

KADIAN® DOSING

- KADIAN® is available in 8 different strengths and can be titrated in 10mg increments. The availability of these 8 doses provides flexibility in dose selection.
- KADIAN® provides convenience and flexibility with once or twice a day dosing.

- KADIAN® doses can be titrated up every other day.

- KADIAN does not have a ceiling or recommended maximal dose, especially in patients with chronic pain of malignancy. In such cases the total dose of KADIAN should be advanced until the desired therapeutic endpoint is reached or clinically-significant opioid-related adverse reactions intervene.

- KADIAN® has no significant food effect and can be administered without regard to meals for dosing convenience.

- KADIAN® is available as an extended release capsule, but it has 3 modes of administration,

    - the capsules can be swallowed whole;

    - the contents of the capsule can be sprinkled on a small amount of applesauce at room temperature or cooler; or

    - The pellet contents of the capsule may be administered through a G-tube.

- **The capsules are to be swallowed whole or the contents sprinkled on applesauce. The pellets in the capsules must not be chewed, crushed, or dissolved due the risk of rapid release and absorption of a potentially fatal dose of morphine.**

Actavis will continue to assist your patients with (1) our Co-pay Assistance Program and (2) our Patient Assistance Program for those patients that cannot afford KADIAN® and qualify.

Do you currently have any KADIAN® Co-Pay Assistance Cards?

How often do you provide your patients with Co-Pay Assistance Cards?

If the HCP uses co-pay cards/ would you like to receive additional co-pay assistance cards?

FAIR BALANCE

Note: If you are unable to complete the discussion of the fair balance information, inform the HCP that a copy of the PI will be sent for the HCP's information and proceed to CLOSE.

As you know, there also are risks associated with the use of KADIAN®.

KADIAN® contains morphine sulfate which is 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®.

KADIAN® 100mg and 200mg 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® is contraindicated in patients with a known sensitivity to morphine or any of its other ingredients, or in any situation where opioids are contraindicated including patients with respiratory depression acute or severe bronchial asthma or hypercarbia. KADIAN® should not be given to patients with gastrointestinal obstruction, particularly those with or suspected of having paralytic ileus.

KADIAN® may be expected to have additive effects when used with alcohol, other opioids, or drugs that cause central nervous system depression including sedatives, hypnotics, anesthetics, phenothiazines, and other tranquilizers.

Respiratory depression is the chief hazard of all morphine preparations and can occur more frequently in elderly or debilitated patients or in patients who also have other respiratory conditions. The effects may be more exaggerated in patients with head injuries or intracranial lesions.

KADIAN® may cause severe hypotension, orthostatic hypotension, and syncope and should be used with caution in patients with circulatory shock

KADIAN® should be discontinued 24 hours before a scheduled cordotomy or other interruption of pain transmission pathways.

KADIAN® should be used with caution in patients with biliary tract disease, including acute pancreatitis.

KADIAN® may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

KADIAN® should only be used in pregnancy if the need for strong opioid analgesia justifies the potential risk to the fetus. KADIAN® is not recommend for use in women during and immediately prior to labor. KADIAN® should not be used in nursing mothers.

KADIAN® has not been studied in patients below the age of 18 years. The range of doses available is not suitable for very young pediatric patients and the apple

sauce sprinkling method of dosing is not an appropriate alternative for these patients.

KADIAN® should be dosed cautiously in elderly patients, usually starting at the low end of the dosing range.

Serious adverse reactions that may be associated with KADIAN® therapy are those observed with other opioid analgesics and include: respiratory depression, respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock.

The most frequent adverse events include drowsiness, dizziness, constipation and nausea.

Please consult the full prescribing information we will be sending you for more information about the benefits and risks associated with KADIAN® that includes sections containing information about "Drug Abuse and Dependence," Overdosage" and "Dosage and Administration." The Dosage and Administration section also contains information about how to convert from other morphine products and other opioid products to KADIAN®.

CLOSE

Based on the information I provided you Dr. _____, can I count on you to prescribe **KADIAN® Capsules** for appropriate patients currently taking EMBEDA®? **(Record Answer)**

Dr. _____, would you be interested in receiving co-pay cards for KADIAN® Capsules?
(Record Answer)

Dr. _____, you will need to write the full name, **KADIAN® Capsules** on the prescription and write "DAW" to ensure your patients receive the product you intended.

Dr._____, on behalf of Actavis and me, thank you for your time. If you have any further questions please feel free to contact us at 1-XXX-XXX-XXXX.

KADIAN®
Morphine Sulfate
Extended-Release Capsules

Revised — February 2010

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

ACTAVIS LOGO

Date

Dr First Name, Last name

Attn:_____
Address1
Address2
City, State, Zip

Dear _____:

Thank you for taking the time to speak with me regarding KADIAN® (morphine sulfate extended-release) Capsules.

As we discussed, there is an announcement on the EMBEDA® (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules CII website that all dosage forms of EMBEDA® have been recalled to the pharmacy level. According to the website, the recall issue is unlikely to pose a safety risk to patients. However, EMBEDA® will be unavailable for some time. The EMBEDA® website advises patients to discuss alternative treatments with their physician.

To help meet the needs of your patients currently taking EMBEDA®, please consider prescribing KADIAN®. Per your request, please find enclosed a conversion guide that provides guidance on how to convert patients from other morphine products to KADIAN®. The guide also provides KADIAN®'s full prescribing information (affixed to the back page). Your request for KADIAN® Prescription Co-Pay Cards will be fulfilled under separate cover. Please be aware that we also provide a Patient Assistance Program at 888-206-9743 for your patients who qualify. We will be following up with you in the near future to ensure that your needs and the needs of your patients continue to be met.

Thank you again for your continuing support. If you have any questions or require additional information, please feel free to contact us at 800-216-1162 or visit our website at www.KADIAN.com.

Best regards,

KADIAN® Sales Representative
Actavis Pharmaceuticals

Enclosed: KADIAN® Conversion Guide
KADI1115-1

Converting from other oral morphine products to KADIAN® (morphine sulfate extended-release) Capsules.

(conversion factor is 1:1)

Do not use this chart for conversion from parenteral (IM/IV) opioid analgesics to KADIAN®.

Morphine daily dose (mg)[a]	Equianalgesic morphine dose (mg)	Suggested total daily KADIAN® dose (mg) administered q24h or in divided doses q12h[b]
30	30	30
60	60	60
90	90	90
100	100	100
200	200	200

[a]Calculate the total daily morphine dose. This amount can be given as KADIAN® capsules in a single daily q24h dose or in divided doses q12h.

[b]Consider giving patients immediate-release (IR) morphine PRN to make up the difference (if the starting dose is less than an equianalgesic dose) until the KADIAN® dose is titrated upward to the needed daily dose.

Sample conversion calculation

1. 60 mg total daily dose of morphine
2. 60 mg daily dose of morphine x 1 (using a 1:1 ratio) = 60 mg daily dose of equianalgesic morphine
3. Suggested total daily dose of KADIAN® = 60 mg
4. Administer KADIAN® capsules as a single dose, 60 mg q24h, or equally divided doses, 30 mg q12h

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

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

Morphine products

- AVINZA® CII (morphine sulfate extended-release capsules) Capsules 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, 120 mg
- Embeda® CII (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg
- KADIAN® CII (morphine sulfate extended-release) Capsules 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200 mg
- MS Contin® CII (morphine sulfate) Tablets 15 mg, 30 mg, 60 mg, 100 mg, 200 mg
- Oramorph® SR CII (morphine sulfate) Sustained Release Tablets 15 mg, 30 mg, 60 mg, 100 mg
- Generic equivalent and other immediate-release products

How to convert from other morphine products to KADIAN®

1. Determine the total daily dose of the current opioid therapy being used. (If both parenteral and oral doses of the same opioid are being given, calculate a separate KADIAN® capsule dose for each and combine)
2. Calculate the conversion of the total daily dose of the current opioid therapy into the equianalgesic morphine dose, using the appropriate ratio (1:1 ratio)
3. Refer to specific analgesic tables on the previous page to find an equianalgesic KADIAN® capsule dose
4. Administer this amount in the most convenient KADIAN® capsule dose strength, either as a single dose q24h or in equally divided doses q12h

Patients on other oral morphine formulations may be converted to KADIAN® by administering one-half of the patient's total daily oral morphine dose as KADIAN® capsules every 12 hours (twice-a-day) or by administering the total daily oral morphine dose as KADIAN® capsules every 24 hours (once-a-day). KADIAN® should not be given more frequently than every 12 hours.

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information for KADIAN® (morphine sulfate extended-release) Capsules.

About this conversion guide

This conversion guide was developed to assist physicians and other healthcare providers when converting patients with moderate to severe chronic pain to an approximate daily starting dose of KADIAN® (morphine sulfate extended-release) Capsules.

The tables included in this booklet are intended for guidance only. The prescriber should determine and adjust the actual dose of KADIAN® on a patient-specific basis.

There is a lack of systematic evidence about these types of analgesic substitutions. Therefore, specific recommendations are not possible. Healthcare professionals are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate.

In general, it is safest to give half of the estimated total daily oral morphine dose as the initial dose and to manage inadequate analgesia by supplementation with IR morphine.

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

KADIAN® CII
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® 20 mg Capsules
KADIAN® 30 mg Capsules
KADIAN® 50 mg Capsules
KADIAN® 60 mg Capsules
KADIAN® 80 mg Capsules
KADIAN® 100 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® (morphine sulfate extended-release) Capsules is contraindicated in any patient who has or is suspected of having paralytic ileus.

Please see Boxed WARNING on this spread, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

Important Safety Information *(continued)*

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.
- 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® (morphine sulfate extended-release) Capsules 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.

continued

- 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® (morphine sulfate extended-release) Capsules 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.

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

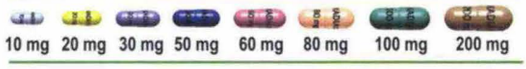
Caution should also be exercised in the administration of KADIAN® to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens, and convulsive disorders.

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 CII

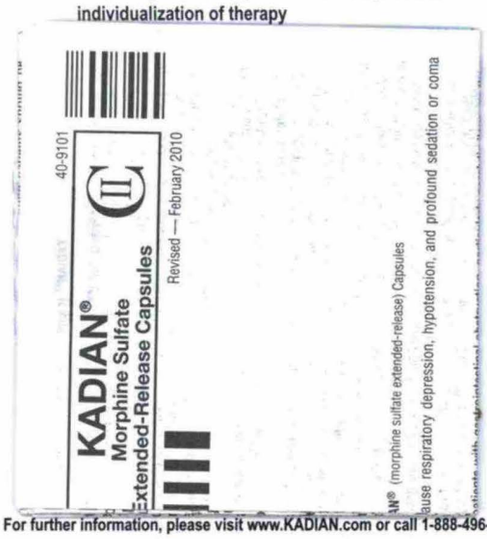
KADIAN® 10 mg Capsules	KADIAN® 60 mg Capsules
KADIAN® 20 mg Capsules	KADIAN® 80 mg Capsules
KADIAN® 30 mg Capsules	KADIAN® 100 mg Capsules
KADIAN® 50 mg Capsules	KADIAN® 200 mg Capsules



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

Capsules are not shown at actual size.

- Dose once or twice daily
- Flexible administration options (capsule, sprinkle, G-tube)
- Polymer-coated pellet technology allows for smooth, consistent plasma concentrations
- No ceiling or recommended maximal dose
- Multiple dosing strengths allow for titration 10 mg at a time
- Frequency of AEs may be minimized by careful individualization of therapy



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

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7 and accompanying Full Prescribing Information.

actavis
creating value in pharmaceuticals

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

40-9101

KADIAN®
Morphine Sulfate
Extended-Release Capsules CII

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

ACTAVIS LOGO

Date

Dr First Name, Last name

Attn:_____
Address1
Address2
City, State, Zip

Dear _____:

Thank you for taking the time to speak with me regarding KADIAN® (morphine sulfate extended-release) Capsules.

As we discussed, there is an announcement on the EMBEDA® (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules CII website that all dosage forms of EMBEDA® have been recalled to the pharmacy level. According to the website, the recall issue is unlikely to pose a safety risk to patients. However, EMBEDA® will be unavailable for some time. The EMBEDA® website advises patients to discuss alternative treatments with their physician.

To help meet the needs of your patients currently taking EMBEDA®, please consider prescribing KADIAN®. Per your request, please find enclosed a conversion guide that provides guidance on how to convert patients from other morphine products to KADIAN®. The guide also provides KADIAN®'s full prescribing information (affixed to the back page). We understand that you do not have a need for KADIAN® Prescription Co-pay cards; however, please be aware that we do provide a Patient Assistance Program at 888-206-9743 for your patients who qualify. We will be following up with you in the near future to ensure that your needs and the needs of your patients continue to be met.

Thank you again for your continuing support. If you have any questions or require additional information, please feel free to contact us at 800-216-1162 or visit our website at www.KADIAN.com.

Best regards,

KADIAN® Sales Representative
Actavis Pharmaceuticals

Enclosed: KADIAN® Conversion Guide
KADI1115-2

Converting from other oral morphine products to KADIAN® (morphine sulfate extended-release) Capsules.

(conversion factor is 1:1)

Do not use this chart for conversion from parenteral (IM/IV) opioid analgesics to KADIAN®.

Morphine daily dose (mg)[a]	Equianalgesic morphine dose (mg)	Suggested total daily KADIAN® dose (mg) administered q24h or in divided doses q12h[b]
30	30	30
60	60	60
90	90	90
100	100	100
200	200	200

[a]Calculate the total daily morphine dose. This amount can be given as KADIAN® capsules in a single daily q24h dose or in divided doses q12h.

[b]Consider giving patients immediate-release (IR) morphine PRN to make up the difference (if the starting dose is less than an equianalgesic dose) until the KADIAN® dose is titrated upward to the needed daily dose.

Sample conversion calculation

1. 60 mg total daily dose of morphine
2. 60 mg daily dose of morphine x 1 (using a 1:1 ratio) = 60 mg daily dose of equianalgesic morphine
3. Suggested total daily dose of KADIAN® = 60 mg
4. Administer KADIAN® capsules as a single dose, 60 mg q24h, or equally divided doses, 30 mg q12h

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

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

Morphine products

- AVINZA® CII (morphine sulfate extended-release capsules) Capsules 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, 120 mg
- Embeda® CII (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg
- KADIAN® CII (morphine sulfate extended-release) Capsules 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200 mg
- MS Contin® CII (morphine sulfate) Tablets 15 mg, 30 mg, 60 mg, 100 mg, 200 mg
- Oramorph® SR CII (morphine sulfate) Sustained Release Tablets 15 mg, 30 mg, 60 mg, 100 mg
- Generic equivalent and other immediate-release products

How to convert from other morphine products to KADIAN®

1. Determine the total daily dose of the current opioid therapy being used. (If both parenteral and oral doses of the same opioid are being given, calculate a separate KADIAN® capsule dose for each and combine)
2. Calculate the conversion of the total daily dose of the current opioid therapy into the equianalgesic morphine dose, using the appropriate ratio (1:1 ratio)
3. Refer to specific analgesic tables on the previous page to find an equianalgesic KADIAN® capsule dose
4. Administer this amount in the most convenient KADIAN® capsule dose strength, either as a single dose q24h or in equally divided doses q12h

Patients on other oral morphine formulations may be converted to KADIAN® by administering one-half of the patient's total daily oral morphine dose as KADIAN® capsules every 12 hours (twice-a-day) or by administering the total daily oral morphine dose as KADIAN® capsules every 24 hours (once-a-day). KADIAN® should not be given more frequently than every 12 hours.

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information for KADIAN® (morphine sulfate extended-release) Capsules.

About this conversion guide

This conversion guide was developed to assist physicians and other healthcare providers when converting patients with moderate to severe chronic pain to an approximate daily starting dose of KADIAN® (morphine sulfate extended-release) Capsules.

The tables included in this booklet are intended for guidance only. The prescriber should determine and adjust the actual dose of KADIAN® on a patient-specific basis.

There is a lack of systematic evidence about these types of analgesic substitutions. Therefore, specific recommendations are not possible. Healthcare professionals are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate.

In general, it is safest to give half of the estimated total daily oral morphine dose as the initial dose and to manage inadequate analgesia by supplementation with IR morphine.

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

KADIAN®

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® 20 mg Capsules
KADIAN® 30 mg Capsules
KADIAN® 50 mg Capsules
KADIAN® 60 mg Capsules
KADIAN® 80 mg Capsules
KADIAN® 100 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® (morphine sulfate extended-release) Capsules is contraindicated in any patient who has or is suspected of having paralytic ileus.

Please see Boxed WARNING on this spread, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

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.
- 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® (morphine sulfate extended-release) Capsules 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.

continued

Important Safety Information *(continued)*

- 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® (morphine sulfate extended-release) Capsules 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.

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

Important Safety Information *(continued)*

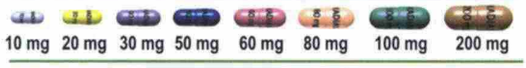
Caution should also be exercised in the administration of KADIAN® to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens, and convulsive disorders.

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.

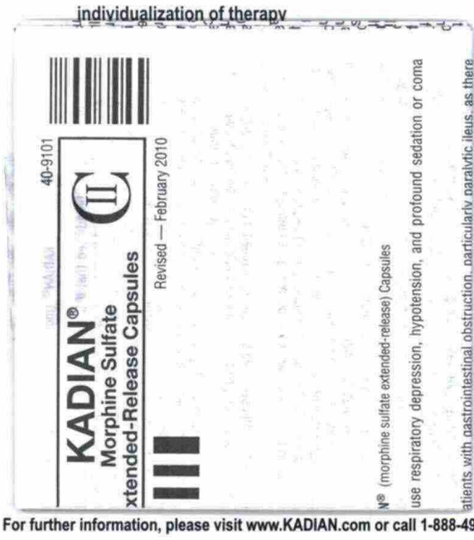
KADIAN®
Morphine Sulfate Extended-Release Capsules C II

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



Capsules are not shown at actual size.

- Dose once or twice daily
- Flexible administration options (capsule, sprinkle, G-tube)
- Polymer-coated pellet technology allows for smooth, consistent plasma concentrations
- No ceiling or recommended maximal dose
- Multiple dosing strengths allow for titration 10 mg at a time
- Frequency of AEs may be minimized by careful individualization of therapy



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

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7 and accompanying Full Prescribing Information.

actavis
creating value in pharmaceuticals

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

40-9101

KADIAN®
Morphine Sulfate
Extended-Release Capsules CII

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

Converting from other oral morphine products to KADIAN® (morphine sulfate extended-release) Capsules.

(conversion factor is 1:1)

Do not use this chart for conversion from parenteral (IM/IV) opioid analgesics to KADIAN®.

Morphine daily dose (mg)[a]	Equianalgesic morphine dose (mg)	Suggested total daily KADIAN® dose (mg) administered q24h or in divided doses q12h[b]
30	30	30
60	60	60
90	90	90
100	100	100
200	200	200

[a]Calculate the total daily morphine dose. This amount can be given as KADIAN® capsules in a single daily q24h dose or in divided doses q12h.

[b]Consider giving patients immediate-release (IR) morphine PRN to make up the difference (if the starting dose is less than an equianalgesic dose) until the KADIAN® dose is titrated upward to the needed daily dose.

Sample conversion calculation

1. 60 mg total daily dose of morphine
2. 60 mg daily dose of morphine x 1 (using a 1:1 ratio) = 60 mg daily dose of equianalgesic morphine
3. Suggested total daily dose of KADIAN® = 60 mg
4. Administer KADIAN® capsules as a single dose, 60 mg q24h, or equally divided doses, 30 mg q12h

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

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

Morphine products

- AVINZA® CII (morphine sulfate extended-release capsules) Capsules 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, 120 mg
- Embeda® CII (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg
- KADIAN® CII (morphine sulfate extended-release) Capsules 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200 mg
- MS Contin® CII (morphine sulfate) Tablets 15 mg, 30 mg, 60 mg, 100 mg, 200 mg
- Oramorph® SR CII (morphine sulfate) Sustained Release Tablets 15 mg, 30 mg, 60 mg, 100 mg
- Generic equivalent and other immediate-release products

How to convert from other morphine products to KADIAN®

1. Determine the total daily dose of the current opioid therapy being used. (If both parenteral and oral doses of the same opioid are being given, calculate a separate KADIAN® capsule dose for each and combine)
2. Calculate the conversion of the total daily dose of the current opioid therapy into the equianalgesic morphine dose, using the appropriate ratio (1:1 ratio)
3. Refer to specific analgesic tables on the previous page to find an equianalgesic KADIAN® capsule dose
4. Administer this amount in the most convenient KADIAN® capsule dose strength, either as a single dose q24h or in equally divided doses q12h

Patients on other oral morphine formulations may be converted to KADIAN® by administering one-half of the patient's total daily oral morphine dose as KADIAN® capsules every 12 hours (twice-a-day) or by administering the total daily oral morphine dose as KADIAN® capsules every 24 hours (once-a-day). KADIAN® should not be given more frequently than every 12 hours.

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information for KADIAN® (morphine sulfate extended-release) Capsules.

About this conversion guide

This conversion guide was developed to assist physicians and other healthcare providers when converting patients with moderate to severe chronic pain to an approximate daily starting dose of KADIAN® (morphine sulfate extended-release) Capsules.

The tables included in this booklet are intended for guidance only. The prescriber should determine and adjust the actual dose of KADIAN® on a patient-specific basis.

There is a lack of systematic evidence about these types of analgesic substitutions. Therefore, specific recommendations are not possible. Healthcare professionals are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate.

In general, it is safest to give half of the estimated total daily oral morphine dose as the initial dose and to manage inadequate analgesia by supplementation with IR morphine.

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

KADIAN® CII
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® 20 mg Capsules
KADIAN® 30 mg Capsules
KADIAN® 50 mg Capsules
KADIAN® 60 mg Capsules
KADIAN® 80 mg Capsules
KADIAN® 100 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® (morphine sulfate extended-release) Capsules is contraindicated in any patient who has or is suspected of having paralytic ileus.

Please see Boxed WARNING on this spread, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

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.
- 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® (morphine sulfate extended-release) Capsules 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.

continued

Important Safety Information *(continued)*

- 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® (morphine sulfate extended-release) Capsules 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.

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7, and accompanying Full Prescribing Information.

Important Safety Information *(continued)*

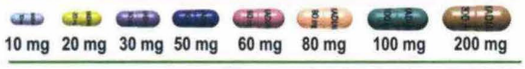
Caution should also be exercised in the administration of KADIAN® to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens, and convulsive disorders.

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

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



Capsules are not shown at actual size.

- Dose once or twice daily
- Flexible administration options (capsule, sprinkle, G-tube)
- Polymer-coated pellet technology allows for smooth, consistent plasma concentrations
- No ceiling or recommended maximal dose
- Multiple dosing strengths allow for titration 10 mg at a time
- Frequency of AEs may be minimized by careful individualization of therapy

40-9101

KADIAN®
Morphine Sulfate
Extended-Release Capsules

Revised — February 2010

N® (morphine sulfate extended-release) Capsules

use respiratory depression, hypotension, and profound sedation or coma

patients with gastrointestinal obstruction, particularly paralytic ileus, as there

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

Please see Boxed WARNING on page 4, Important Safety Information on pages 4-7 and accompanying Full Prescribing Information.

actavis
creating value in pharmaceuticals

KADI1107

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

Printed in USA

40-9101

KADIAN®
Morphine Sulfate
Extended-Release Capsules

CII

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

3 LBS PAK 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 9339 4174

BILLING: P/P

Reference#1: 20-616 KADIAN (multiple)
Reference#2: 90-370 Valacyclovir (profes/consum)
UIS 13.1.13. WXPIE80 12.0A 01/2011

Proof of Delivery

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Dear Customer,

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

Tracking Number:	1Z0620770193394174
Reference Number(s):	20-616 KADIAN (MULTIPLE), 90-370 VALACYCLOVIR (PROFES/CONSUM)
Service:	UPS Next Day Air®
Weight:	3.00 lbs
Shipped/Billed On:	03/29/2011
Delivered On:	03/30/2011 9:29 A.M.
Delivered To:	5901 AMMENDALE RD BELTSVILLE, MD, US 20705
Signed By:	HILL
Left At:	Dock

Thank you for giving us this opportunity to serve you.

Sincerely,

UPS

Tracking results provided by UPS: 03/30/2011 11:39 A.M. ET

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