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: 11/18/2010

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: 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 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:
POT	11/10/10	KADIAN Dosing Guide Part # KADI1007	N/A	

Add Continuation Page

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Terri Nataline, J.D., R.A.C.
Vice President, Regulatory and Medical Affairs

10. SIGNATURE OF RESPONSIBLE OFFICIAL
Adriene Talmore for

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

12. RESPONSIBLE OFFICIAL'S
a. PHONE NO.
(908) 659-2317
b. FAX NO.
(908) 659-2250

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

FORM FDA 2253 (6/08) PREVIOUS EDITION IS OBSOLETE. Page 1 of 3

PSC Graphics (301) 443-1090 EF

MLG CSR 11976
11/18/2021
Robin Hagy
Exh. 13

PLAINTIFFS TRIAL EXHIBIT
P-21971_00001

FILE COPY

actavis
creating value in pharmaceuticals

November 18, 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 Dosing Guide
KADI1007

If you have any questions relating to this submission, please do not hesitate to contact the undersigned at (908) 659-2317, fax number (908) 659-2250, or via secure email to RegulatoryAffairsUS@actavis.com.

Sincerely,
ACTAVIS ELIZABETH LLC

Terri Nataline, J.D., R.A.C.
Vice President,
Regulatory and Medical Affairs

TN/cch
Enclosures

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

KADIAN®

Morphine Sulfate Extended-Release Capsules

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

Dosing Guide

Please see Boxed WARNING on page 2 and Important Safety Information on pages 3-5, and accompanying Full Prescribing Information.

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.

Please see Boxed WARNING on this page and Important Safety Information on pages 3-5, and accompanying Full Prescribing Information.

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 cor pulmonale, and in patients having a substantially decreased respiratory reserve (e.g. severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea. 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

continued

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 over sedation 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.

Please see Boxed WARNING on page 2 and Important Safety Information on pages 3-5, and accompanying Full Prescribing Information.

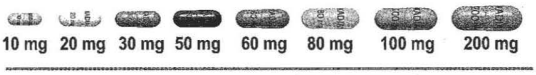
- KADIAN® should be administered with caution, and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; patients with Addison's disease; myxedema; hypothyroidism; prostatic hypertrophy or urethral stricture.

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.

Flexible dosing to help meet individual patient needs

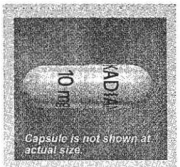


Capsules are not shown at actual size.

- Available in 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg capsules
- The 100 mg and 200 mg capsules are for use only in opioid-tolerant patients.

Flexible administration options

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 or cooler 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.

Use of KADIAN® as the First Opioid Analgesic

There has been no evaluation of KADIAN® as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient to adequate analgesia using an extended-release morphine, it is ordinarily advisable to begin treatment using an immediate-release morphine formulation.

Please see Boxed WARNING on page 2 and Important Safety Information on pages 3-5, and accompanying Full Prescribing Information.

Initiating Therapy with KADIAN® Capsules

It is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of KADIAN®, attention should be given to:

1) the total daily dose, potency, and kind of opioid the patient has been taking previously;

2) the reliability of the relative potency, estimate used to calculate the equivalent dose of morphine needed

(Note: potency estimates may vary with the route of administration);

3) the patient's degree of opioid experience and opioid tolerance;

4) the general condition and medical status of the patient;

5) concurrent medication;

6) the type and severity of the patient's pain.

Care should be taken to use low initial doses of KADIAN® in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications.

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 pre-emptive analgesia (administration pre-operatively for the management of post-operative pain), or for pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in these settings has not been established.

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.

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

Individualization of Dosage

- **Administer one-half of the estimated total daily oral morphine dose every 12 hours (twice-a-day).**

or

- **Administer the total daily oral morphine dose every 24 hours (once-a-day).**

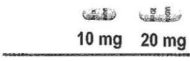
- **Titrate no more frequently than every-other-day to allow the patient to stabilize before escalating the dose.**

If breakthrough pain occurs, the dose may be supplemented with a small dose (less than 20% of the total daily dose) of a short-acting analgesic. Patients who are excessively sedated after a once-a-day dose or who regularly experience inadequate analgesia before the next dose should be switched to twice-a-day dosing.

KADIAN® is a third-step drug which is most useful when the patient requires a constant level of opioid analgesia as a "floor" or "platform" from which to manage breakthrough pain. When a patient has reached the point where comfort cannot be provided with a combination of non-opioid medications (NSAIDs and acetaminophen) and intermittent use of moderate or strong opioids, the patient's total opioid therapy should be converted into a 24-hour oral morphine equivalent.

Please see Boxed WARNING on page 2 and Important Safety Information on pages 3-5, and accompanying Full Prescribing Information.

Initiating Therapy in Patients without Proven Opioid Tolerance



10 mg 20 mg Capsules are not shown at actual size.

- **Start only on the 10 mg or 20 mg strength.**

- **Increase at a rate not greater than 20 mg every-other-day.**

- **Adjust dosage until they have achieved their individual best balance between baseline analgesia and opioid side effects such as confusion, sedation, and constipation.**

- **Total dose should be advanced until the desired therapeutic endpoint is reached or clinically significant opioid-related adverse reactions intervene.**

Considerations in the Adjustment of Dosing Regimens

If signs of excessive opioid effects are observed early in the dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia–that is, if breakthrough pain occurs when KADIAN® is administered on an every 24-hours dosing regimen– consideration should be given to dosing every 12-hours. If breakthrough pain occurs on a 12 hour dosing regimen a supplemental dose of a short-acting analgesic may be given. As experience is gained, adjustments in both dose and dosing interval can be made to obtain an appropriate balance between pain relief and opioid side effects. To avoid accumulation the dosing interval of KADIAN® should not be reduced below 12 hours.

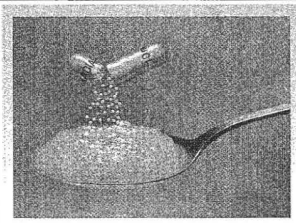
Cessation of Therapy

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

Alternative Methods of Administration

In a study of healthy volunteers, KADIAN® pellets sprinkled over apple sauce were found to be bioequivalent to KADIAN® capsules swallowed whole with apple sauce under fasting conditions. Other foods have not been tested. Patients who have difficulty swallowing whole capsules or tablets may benefit from this alternative method of administration.



sprinkled over apple sauce

Capsule is not shown at actual size.

1) Sprinkle the pellets onto a small amount of apple sauce. Apple sauce should be room temperature or cooler.

2) The patient must be cautioned not to chew the pellets which could result in the immediate release of a potentially dangerous, even fatal, dose of morphine.

3) Use immediately.

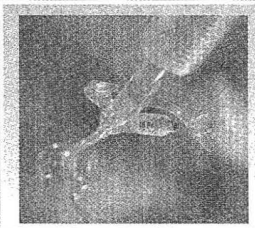
4) Rinse mouth to ensure all pellets have been swallowed.

5) Patients should consume entire portion and should not divide apple sauce into separate doses.

Please see Boxed WARNING on page 2 and Important Safety Information on pages 3-5, and accompanying Full Prescribing Information.

Alternative Methods of Administration *(continued)*

The entire capsule contents may alternatively be administered through a 16 French gastrostomy tube.



gastrostomy tube

1) Flush the gastrostomy tube with water to ensure that it is wet.

2) Sprinkle the KADIAN® Pellets into 10 mL of water.

3) Use a swirling motion to pour the pellets and water into the gastrostomy tube through a funnel.

4) Rinse the beaker with a further 10 mL of water and pour this into the funnel.

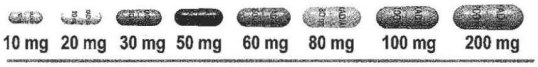
5) Repeat rinsing until no pellets remain in the beaker.

THE ADMINISTRATION OF KADIAN® PELLETS THROUGH A NASOGASTRIC TUBE SHOULD NOT BE ATTEMPTED.

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

KADIAN® CII
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



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

℞ 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.

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For further information, please visit www.KADIAN.com or call 1-888-496-3082.
Please see accompanying Full Prescribing Information.

Reference: KADIAN® CII [prescribing information]. Morristown, NJ: Actavis Elizabeth LLC. 2010.

actavis
creating value in pharmaceuticals

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

KADI1007
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

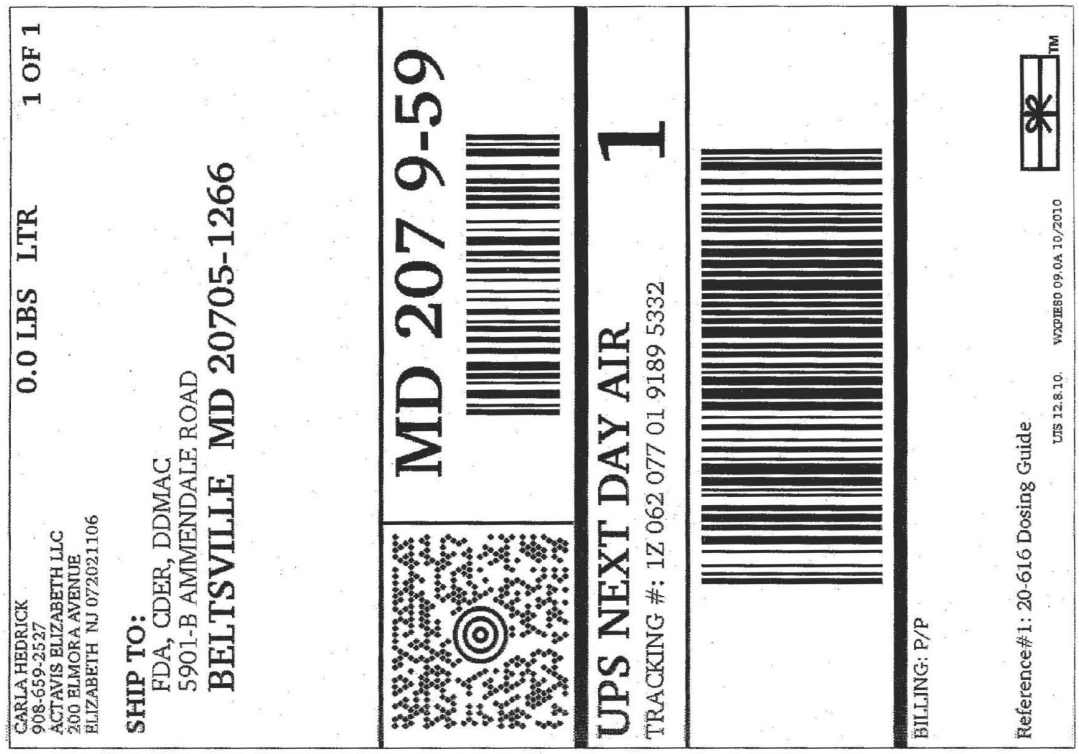
KADIAN® should not be given to patients with gastrointestinal obstruction, particularly paralytic ileus, as there is a risk of the product remaining in the stomach for an extended period and the subsequent release of a bolus of morphine when normal gut motility is restored. As with other solid morphine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

Other

Although extremely rare, cases of anaphylaxis have been reported.

PRECAUTIONS

General

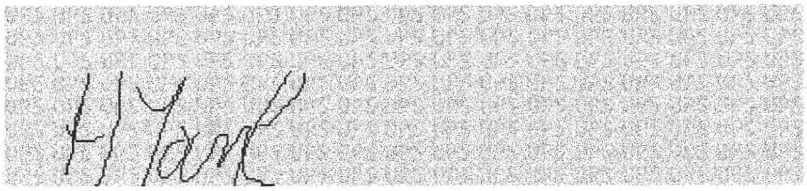


Proof of Delivery

Dear Customer,

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

Tracking Number:	1Z0620770191895332
Reference Number(s):	20-616 DOSING GUIDE
Service:	NEXT DAY AIR
Shipped/Billed On:	11/18/2010
Delivered On:	11/19/2010 9:07 A.M.
Delivered To:	5901 AMMENDALE RD BELTSVILLE, MD, US 20705
Signed By:	YOUNG



Location:	RECEIVER

Thank you for giving us this opportunity to serve you.

Sincerely,

UPS

Tracking results provided by UPS: 11/22/2010 10:38 A.M. ET