From: Terri Nataline
Sent: Friday, July 23, 2010 11:30 AM
To: 'mfogelso@kai-research.com'
Subject: Fw: DDMAC Warning Letter Correspondence KADIAN
Attachments: 10-04-09 Response to FDA.pdf; 10-04-19 FDA Response.pdf; 10-05-03 Response to FDA.pdf; 10-05-20 FDA Response.pdf; 10-06-10 Response to FDA.pdf; 10-07-06 FDA Response.pdf; 10-07-16 Response to FDA.pdf; 10-02-18 FDA Warning Letter.pdf; 10-03-04 Response to Warning Letter.pdf; 10-03-05 Amendment to Response.pdf; 10-03-26 FDA Response.pdf

----- Original Message -----
From: Terri Nataline
To: 'Miriam Fogelson' <mfogelso@kai-research.com>
Sent: Thu Jul 22 15:39:35 2010
Subject: DDMAC Warning Letter Correspondence KADIAN

Miriam,

Here is the correspondence between FDA and Actavis regarding the Kadian. Hopefully it doesn't crash your computer. I will check my calendar and give you availability for next week.

10-04-09 Response to FDA
10-04-19 FDA Response
10-05-03 Response to FDA
10-05-20 FDA Response
10-06-10 Response to FDA
10-07-06 FDA Response
10-07-16 Response to FDA
10-02-18 FDA Warning Letter
10-03-04 Response to Warning Letter
10-03-05 Amendment to Response
10-03-26 FDA Response

Note: To protect against computer viruses, e-mail programs may prevent sending or receiving certain types of file attachments. Check your e-mail security settings to determine how attachments are handled.

PLAINTIFF TRIAL EXHIBIT
P-02386_00001

EXHIBIT Boothe
WIT: Allergan 30
DATE: 1-17-19
Marie Foley, RMR, CRR

actavis
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FILE COPY

Confidential -- Not For Public Disclosure

April 9, 2010

VIA OVERNIGHT MAIL DELIVERY

Thomas Abrams, RPh, MBA
Director
Division of Drug Marketing, Advertising, and Communications
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 20-616
Kadian® (morphine sulfate extended-release) Capsules,
MACMIS #18148

Dear Mr. Abrams,

Reference is made to the February 18, 2010 Warning Letter from the Division of Drug Marketing, Advertising, and Communications (DDMAC) for Kadian®. Further reference is made to the corrective actions Actavis Elizabeth LLC ("Actavis") proposed in its March 4, 2010 letter and DDMAC's subsequent March 26, 2010 response. In its response, DDMAC requested, among other things, that Actavis clarify certain points in its proposed dissemination plan and modify the text in its proposed Dear Healthcare Professional (DHP) and Dear Consumer letters.

Accordingly, Actavis is proposing to revise its dissemination plan and letters to address all of the points raised in DDMAC's March 26, 2010. The details of these revisions are provided below.

Revised Dissemination Plan

DDMAC Request

- We acknowledge your confirmation that approximately 3,940 copies of the Comparison Detailer were distributed to physician's between June 2009 and February 2010. We also acknowledge your proposal to mail DHP letters to 1,900 physicians in the Actavis database of target physicians for its sales force. We request that you confirm that the 1,900 physicians in your database include all physicians that could have been exposed to the Comparison Detailer.

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

Actavis Response

Actavis can state with a high degree of confidence that the 1,900 physicians in its database encompasses all of the physicians that could have been exposed to the Comparison Detailer. When it created the database, Actavis made every effort to ensure that it included all of the healthcare professionals at a single location (i.e. all healthcare professionals in the group practice or clinic). The Actavis sales representatives were instructed to use the database to identify the individuals they would visit and were advised that they would be compensated for only those prescriptions written by the healthcare professionals contained in this database. As a result, there was no incentive for the sales force to make visits to "unlisted" healthcare professionals. Therefore, only those individuals listed in the database would have had the opportunity for exposure to the Comparison Detailer. Finally, as Actavis previously noted in its March 4, 2010 letter, this database remains unchanged since its implementation.

DDMAC Request

- We acknowledge your confirmation that approximately 170,000 brochures were distributed to consumers between January 2009 and February 2010 through telephone registration, web site registration, and physician distribution. We also acknowledge that approximately 6.5% of the Co-Pay Assistance Program Cards were redeemed. We request clarification as to whether you are able to directly contact patients who redeemed the Co-Pay Assistance Program Cards to ensure that these patients receive Dear Consumer Letters.

Actavis Response

While Actavis has the names of the patients that redeemed the Co-Pay Assistance Program Cards, it only has the mailing addresses for those patients that received cards directly from Actavis either through telephone or website registration. Actavis does not have the addresses of those individuals who received the Co-Pay Cards directly from the healthcare professional. Thus, Actavis is proposing to mail the Dear Consumer Letter to all patients that received the Co-Pay Assistance Program Cards directly from Actavis (e.g. for patients that provided a mailing address) regardless of whether the patient redeemed the card. To ensure that the remaining patients receive the Dear Consumer Letter, Actavis is proposing to distribute the letters to the physicians' offices for further dissemination as described below.

DDMAC Request

- We acknowledge your proposal to mail the Dear Consumer letters to (1) consumers who received the brochure as a mailer through website registration or telephone registration, and (2) consumers who used the Co-Pay Assistance Program Card but do not fall into the first category. To address consumers who fall into the second category, you propose to distribute the Dear Consumer letters to physicians' offices and request that physicians provide the Dear Consumer letter to any patients who may have received the brochure and to place the Dear Consumer letters in office waiting rooms. We have reviewed your proposal and additionally recommend that the Dear Consumer letters that are distributed

to physicians' offices be included in a display stand with a prominent statement to draw attention to consumers as to the type of material contained within. In addition, we would like clarification as to the number of Dear Consumer letters that will be distributed to each physician's office.

Actavis Response

As requested, Actavis will provide to each physician's office a display stand that holds the Dear Consumer Letters. The display stand will provide the statement on the front panel: "Important Correction of Drug Information for Kadian® (morphine sulfate extended-release) Capsules" in a prominent manner. The formatting will be consistent with Actavis' proposed envelope that will accompany the DHP and Dear Consumer letters. (See Attachment 1).

The number of Dear Consumer letters that Actavis proposes to distribute to each physician's office will be based on the number of patients per physician that used a co-pay card. Thus, the number of letters that Actavis proposes to distribute follows below:

Number of Patients per Physician Who Have Used a Co-Pay Card	Number of Letters Provided to Physician for Dissemination to Patient	Number of Letters Provided in Display Stand
2 or fewer patients	2	2
3-5 patients	3	5
6-10 patients	3	10
11-20 patients	5	20
21-50 patients	5	50
>50 patients	10	100

Dear Healthcare Professional (DHP) Letter

Actavis has modified the message in its proposed DHP letter based on the comments provided in DDMAC's March 26, 2010 response. The revised DHP letter is provided in Attachment 2 for review.

Dear Consumer Letter

Actavis has modified the message in its proposed Dear Consumer letter based on the comments and revisions provided in DDMAC's March 26, 2010 response. The revised Dear Consumer letter is provided in Attachment 3 for review.

NDA 20-616
Kadian® (morphine sulfate extended-release) Capsules, CII
MACMIS #18148

General Comments

Actavis acknowledges DDMAC's general comments. To that end, please be advised that Actavis has revised both the DHP and Dear Consumer letters to include the signature line for Doug Boothe, Chief Executive Officer for Actavis US. The letters will be accompanied by the proposed envelope provided in Attachment 1. This envelope is consistent with the formatting requirements set forth in 21 C.F.R. § 200.5. A copy of the full prescribing information for Kadian will be provided with each DHP and Dear Consumer letter.

Actavis appreciates DDMAC's comments and suggestions for improving Actavis' corrective messages. Actavis trusts that you will find that the revised dissemination plan and proposed letters address all of the points raised in the March 26, 2010 DDMAC response.

Please do not hesitate to contact me at 908-659-2317 if you have questions.

Sincerely,

Terri Nataline
Vice President, Regulatory and Medical Affairs
Actavis US

Enclosures

cc: Elaine Hu Cunningham, Pharm. D., Senior Regulatory Review Officer
CDER, DDMAC Communications
(via facsimile: 301-847-8444)

Doug Boothe
Chief Executive Officer
Actavis US

ATTACHMENT 1

Actavis Kadian LLC
60 Columbia Road, Bldg. B
Morristown NJ 07960 USA

IMPORTANT CORRECTION OF DRUG INFORMATION

ATTACHMENT 2

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IMPORTANT:
Correction of Drug Information about
KADIAN® (morphine sulfate extended-release) Capsules, CII

April __, 2010

Dear Healthcare Professional,

Between March 2009 and December 2010, Actavis US ("Actavis") sales representatives, during office visits with physicians, distributed a certain material to promote Kadian that was the subject of a Warning Letter (dated February 18, 2010) issued by the U.S. Food and Drug Administration ("FDA"). The cover page of this material read: "Why settle for generic MS Contin® tablets..."

In the Warning Letter, FDA raised the following concerns regarding the material: (1) it omitted and minimized serious risks associated with Kadian; (2) it broadened Kadian's indication and failed to present limitations to its approved indication; and (3) it presented unsubstantiated superiority claims. Upon receiving this letter, Actavis immediately ceased using or distributing this material.

Actavis would like to take the opportunity to correct and clarify the statements and representations made in this specific promotional material. Please note that the issues discussed below apply to other Kadian promotional materials distributed during this time period, including: (1) the Kadian Visual Aid; (2) a Kadian Conversion Guide; and (3) a material titled "Behind the Scenes, the KADIAN Capsules Story." Actavis has also ceased using or distributing these materials.

I. Broadening of Indication/Failure to State Full Indication

FDA objected to certain representations in the material, stating that these representations suggested that Kadian is appropriate to treat broad types of chronic pain.

Please see below the full indication statement for Kadian, including limitations on use, as reflected in the Indications and Usage section of the full Prescribing Information:

> 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 (see **CLINICAL PHARMACOLOGY**).
>
> **KADIAN® Capsules are NOT intended for use as a prn analgesic.**

Actavis, Inc. | 60 Columbia Rd., Bldg. B Morristown, NJ 07960 | t (973) 993-4501 | www.actavis.com

KADIAN® is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. KADIAN® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

II. Omission and Minimization of Risk Information

FDA stated that while the material disclosed certain risks (including information on the boxed warning), the material failed to include other important and serious risk information.

Please see below the most important and serious risks associated with Kadian, and please refer to the enclosed full Prescribing Information for additional discussion of these risks:

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.

Other important and serious risks associated with Kadian include:

Contraindictions:

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.

Warnings:

KADIAN® Capsules are to be swallowed whole and are not to be chewed, crushed, or dissolved. Taking chewed, crushed, or dissolved KADIAN® Capsules leads to rapid release and absorption of a potentially fatal dose of morphine.

KADIAN® 100 mg and 200 mg Capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. This capsule strength may cause fatal respiratory depression when ingested or administered to patients who are not previously exposed to opioids.

Care should be taken in the prescribing of this capsule strength. 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.

Misuse, Abuse and Diversion of Opioids
KADIAN® contains morphine an opioid agonist and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Morphine 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.

Abuse of KADIAN® by crushing, chewing, snorting or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND DEPENDENCE** sections in the full Prescribing Information)

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse
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.

Impaired Respiration
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.

Head Injury and Increased Intracranial Pressure
The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. 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.

Hypotensive Effect
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 also **PRECAUTIONS - Drug Interactions**.) 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.

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
KADIAN® is intended for use in patients who require continuous, around-the-clock opioid analgesia for an extended period of time. As with any potent opioid, it is critical to adjust the dosing regimen for KADIAN® for each patient, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of the initial dose of KADIAN®, attention should be given to the points under **DOSAGE AND ADMINISTRATION**.

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.

Selection of patients for treatment with KADIAN® should be governed by the same principles that apply to the use of any potent opioid analgesics. Specifically, the increased risks associated with its use in the following populations should be considered: the elderly or debilitated and those with severe impairment of hepatic, pulmonary, or renal function; hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychosis; prostatic hypertrophy, or urethral stricture; acute alcoholism; delirium tremens; kyphoscoliosis, or inability to swallow.

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.

Cordotomy
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.

Use in Pancreatic/Biliary Tract Disease
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 and Physical Dependence
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.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy** in the full Prescribing Information).

Special Risk Groups
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.

Driving and Operating Machinery
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** in the full Prescribing Information)

III. Unsubstantiated Superiority Claims and Unsubstantiated Effectiveness Claims

FDA objected to several claims in the material that reference MS Contin® (morphine sulfate controlled-release) Tablets, CII, Avinza® (morphine sulfate extended-release), Capsules, CII, and generic controlled-release morphine tablets. Specifically, the material:

- Stated "Why settle for generic MS Contin® tablets…When you can prescribe the benefits of KADIAN® capsules."

- Made claims regarding the superior pharmacokinetic properties of Kadian versus generic controlled-release morphine tablets which implied that Kadian will lead to less breakthrough pain and more consistent pain relief.

- Made claims regarding "better pain control and improved sleep scores" versus generic controlled-release morphine tablets.

- Made claims about the superior dosing flexibility of Kadian versus MS Contin and Avinza which implied that Kadian offers fewer barriers to prescribing compared to MS Contin or Avinza.

FDA objected to each of the above claims as misleading, and objected to any representation in the distributed material that Kadian is safer or more effective than these other products because the references cited in support of these claims do not represent substantial evidence or substantial clinical experience. FDA is not aware of any evidence demonstrating that Kadian treatment results in less breakthrough pain, more consistent pain relief, or fewer barriers to prescribing than any other approved extended-release morphine product.

******

Please see the enclosed full Prescribing Information for Kadian.

If you have any questions, please call 1-877-637-4629.

Sincerely,

Doug Boothe
Chief Executive Officer
Actavis US

ATTACHMENT 3

actavis
creating value in pharmaceuticals

IMPORTANT:
Correction of Drug Information about
KADIAN® (morphine sulfate extended-release) Capsules, CII

April__, 2010

Dear Valued Consumer,

You are receiving this letter because you may have received from Actavis US ("Actavis") a Co-Pay Assistance Program Card which was attached to a Co-Pay Assistance Program Brochure. This letter specifically concerns the Co-Pay Assistance Program Brochure ("Brochure"), which was the subject of a Warning Letter issued by the U.S. Food and Drug Administration ("FDA") on February 18, 2010.

In the Warning Letter, FDA raised the following concerns about the Brochure: (1) it left out and minimized serious risks associated with Kadian; (2) it claimed Kadian was approved by FDA for conditions it is not approved for; and (3) it presented unsupported claims about how well it works.

Actavis would like to take the opportunity to correct and clarify the statements and representations about Kadian made in the Brochure.

I. Indication

FDA objected to the general discussion in the Brochure regarding "chronic pain" and "pain management," stating that this discussion suggested that Kadian is appropriate to treat all types of chronic pain.

Please note that Kadian is indicated to treat only certain types of pain. Specifically:

> KADIAN® capsules are an extended-release capsule taken by mouth of morphine sulfate that is used to manage moderate to severe pain that continues around-the-clock and is expected to last for an extended period of time.
>
> **KADIAN® is NOT for use to treat pain that occurs once in a while ("as needed").**
>
> KADIAN® is not indicated for pain in the immediate post-operative period (12-24 hours following surgery) for patients who have not taken drugs called opioids before.
>
> KADIAN® is not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

Please remember to consider the above information about the appropriate use of Kadian, including its limitations on use, and discuss these issues with your doctor.

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FOR REVIEW PURPOSES ONLY
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II. Risks

FDA stated that while the Brochure mentioned certain risks associated with Kadian (including information on its boxed warning (see below)), the Brochure failed to include other important and serious risk information. Moreover, FDA objected to the Brochure's use of medical language to explain these risks to patients because such information may not be easily understood.

Please see below a discussion of the most important and serious risks associated with Kadian, and please refer to the enclosed full Prescribing Information for additional discussion of these risks.

A. In The FDA Approved Prescribing Information for Healthcare Providers:

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.

B. What This Means for You:

Most Important Information to Know About Kadian

- Kadian, which is a federally controlled substance (CII), can be abused by people who abuse prescription medicines or street drugs. To prevent theft, misuse, or abuse of KADIAN®, keep it in a safe place. Do not give Kadian to anyone else. It may harm them or even cause death. After you stop taking Kadian, flush any unused capsules down the toilet.

- Do not crush, dissolve, or chew Kadian capsules or the capsule contents before swallowing. Abuse of Kadian by crushing, chewing, snorting or injecting the dissolved product will result in the uncontrolled delivery of morphine and pose a significant risk to the abuser that could result in overdose or death.

- KADIAN® is **NOT** for use to treat pain that occurs once in a while ("as needed").

- Kadian 100 mg and 200 mg capsules are for use only in opioid tolerant patients. "Opioid tolerant" means that you regularly use another opioid medicine for constant pain and that your body is used to it. **Ingesting Kadian 100 mg and 200 mg capsules when you are not opioid tolerant may cause serious breathing problems and death.**

Do Not Take Kadian If:

- You have a known hypersensitivity (allergy) to morphine, morphine salts, or any of the ingredients in Kadian (See the accompanying Prescribing Information for a complete list of ingredients in Kadian).

- You are having an asthma attack or have severe asthma, trouble breathing, or lung problems.

- You have a bowel blockage called paralytic ileus.

- Do not take Kadian with alcohol, other opioids, or illicit drugs because dangerous additive effects may occur resulting in serious injury or death. In addition, alcohol can cause very high levels of morphine in your blood and you can die due to an overdose of morphine.

Possible Side Effects of Kadian

- Kadian can cause serious breathing problems that may be life-threatening, especially if Kadian is used in the wrong way. Call your healthcare professional or get medical help right away if your breathing slows down, you have shallow breathing, you feel faint, dizzy, confused, or have any unusual symptoms. These can be symptoms that you have taken too much Kadian or that the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

- Kadian can cause physical dependence. Do not stop taking Kadian or any other opioid without talking to your healthcare professional. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addition. Your doctor can tell you more about the differences between physical dependence and drug addiction.

- There is a chance of abuse or addiction with Kadian.

- Serious allergic reactions, while extremely rare, have been reported with use of Kadian. Get medical help right away if you experience any symptoms of a severe allergic reactions, such as: feeling dizzy or faint, trouble breathing, chest pain, or swelling of the face, throat, or tongue.

- Do not drive or operate machinery or perform other potentially hazardous activities until you know how you react to this medicine or a change in the dose.

Please Remember

- These are not all the risks and side effects associated with Kadian. For more information, please contact your doctor.

- Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

III. Unsubstantiated Effectiveness Claims

FDA objected to the following statements in the Brochure regarding chronic pain:

- ". . . Many Americans suffer from chronic or ongoing pain. It can cause you to miss work and can even keep you from enjoying life. If left untreated, pain can place stress on your body and your mental health . . . ."

- " . . . Chronic pain . . . can be inconvenient and can keep you from your daily tasks."

FDA stated that the above representations suggested that use of Kadian results in a positive impact on a patient's work, physical and mental functioning, daily activities, or enjoyment of life. FDA stated that these representations were misleading because they suggested that Kadian is more effective than has been demonstrated. FDA is not aware of any evidence demonstrating that Kadian treatment results in a positive impact in these areas.

******

Please see the enclosed full Prescribing Information for Kadian. If you have any questions regarding Kadian or this letter, please consult with your doctor or call 1-877-637-4629.

Sincerely,

Doug Boothe
Chief Executive Officer
Actavis US

actavis
creating value in pharmaceuticals

Fax message

To	Elaine Hu Cunningham, Pharm. D., Senior Regulatory Review Officer		
Date	04/09/2010	Fax No	301-847-8444
No of pages (including this one)	20		
Subject	MACMIS #18148		
From	Terri Nataline, Vice President, Regulatory and Medical Affairs		

********** -COMM. JOURNAL- ********** DATE APR-09-2010 ***** TIME 02:45 ********

MODE = MEMORY TRANSMISSION START=APR-09 02:41 END=APR-09 02:45

FILE NO.=676

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	☎	913018478444	020/020	00:03:34

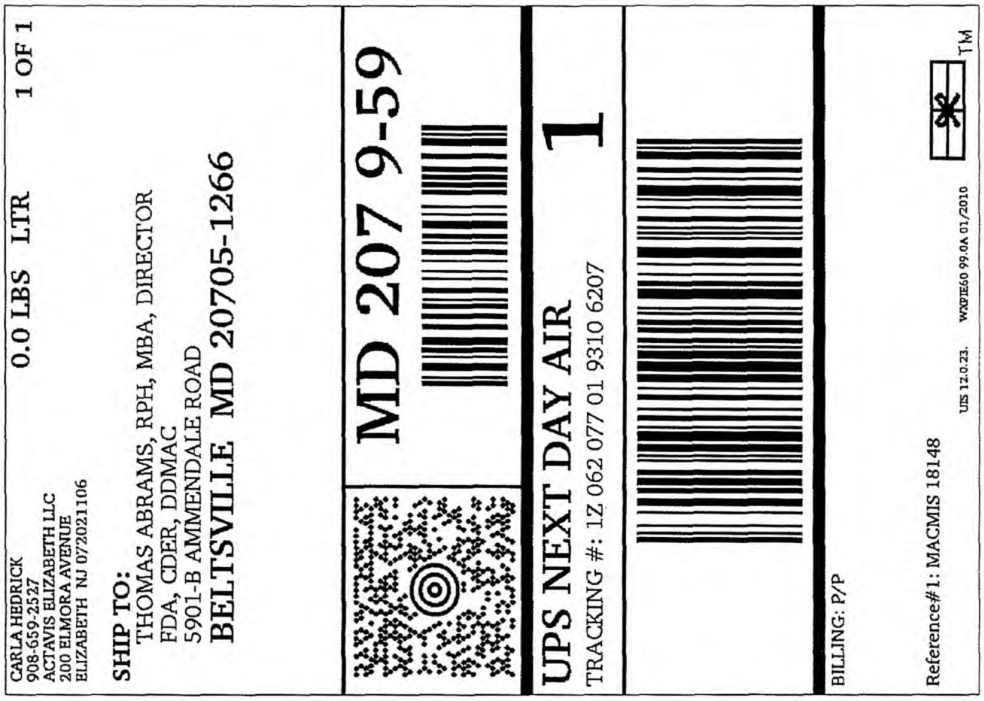
-ACTAVIS -

********** -REGULATORY AFF - ***** - 908 659 2250- **********

actavis
creating value in pharmaceuticals

Fax message

To	Elaine Hu Cunningham, Pharm. D., Senior Regulatory Review Officer		
Date	04/09/2010	Fax No	301-847-8444
No of pages (including this one)	20		
Subject	MACMIS #18148		
From	Terri Nataline, Vice President, Regulatory and Medical Affairs		



Proof of Delivery

Dear Customer,

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

Tracking Number:	1Z0620770193106207
Reference Number(s):	MACMIS 18148
Service:	NEXT DAY AIR
Shipped/Billed On:	04/09/2010
Delivered On:	04/12/2010 8:38 A.M.
Delivered To:	5901 AMMENDALE RD BELTSVILLE, MD, US 20705
Signed By:	MANG
Location:	RECEIVER

Thank you for giving us this opportunity to serve you.

Sincerely,

UPS

Tracking results provided by UPS: 04/12/2010 9:59 A.M. ET

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Terri Nataline
Vice President, Regulatory and Medical Affairs
Actavis US
60 Columbia Road, Building B
Morristown, NJ 07960

RE: NDA 020616
Kadian® (morphine extended-release) Capsules, CII
MACMIS #18148

Dear Ms. Nataline:

This letter responds to Actavis Elizabeth LLC's (Actavis) April 9, 2010, letter submitted to the Division of Drug Marketing, Advertising, and Communications (DDMAC) in response to DDMAC's March 26, 2010, letter requesting clarification and revisions to Actavis's March 4, 2010, proposed dissemination plan, Dear Healthcare Professional (DHP) letter, and Dear Consumer letter. Reference is made to the February 18, 2010, DDMAC Warning Letter for Kadian® (morphine extended-release) Capsules, CII (Kadian).

We appreciate the steps that you have taken thus far to address the issues outlined in the Warning Letter and our letter dated March 26, 2010. We have reviewed your responses and proposed revisions in your April 9, 2010 letter and offer the following comments.

Dissemination Plan

- We appreciate your confirmation that the 1,900 physicians in the Actavis database encompass all of the physicians that could have been exposed to the Comparison Detailer. Therefore, we have no further comments on your proposal to mail the DHP letters to the 1,900 physicians in the Actavis database of target physicians.

- We acknowledge your proposal to mail Dear Consumer letters to all patients that received the Co-Pay Assistance Program Brochure and/or Co-Pay Assistance Cards directly from Actavis regardless of whether the patient redeemed the card. We have reviewed your proposal and have no further comments at this time.

  For the remaining patients for whom you do not have addresses for, you propose to distribute the Dear Consumer letters to physicians' offices. We acknowledge that you propose to provide each physician's office with a display stand that will hold the Dear Consumer letters. You propose a display stand that will include the following prominent statement on the front panel: "Important Correction of Drug Information for Kadian® (morphine sulfate extended-release) Capsules." You state that the formatting of this statement will be consistent with the proposed envelope that will accompany the

DHP and Dear Consumer letters. We reviewed your proposal regarding the display stand and have no further comments at this time.

In addition, you propose to distribute a number of Dear Consumer letters based upon the number of patients per physician that used a co-pay card (e.g., if two or fewer patients used a co-pay card for a physician, Actavis proposes to distribute two copies of the Dear Consumer letter to the physician and two copies to be provided in the display stand at the physician's office). However, we feel that this proposed dissemination of the Dear Consumer letter at the physician's office may not necessarily reach all of the patients who could have been exposed to the Co-Pay Assistance Program Brochure and/or Co-Pay Assistance Card. Therefore, in addition to the copies of the Dear Consumer letter to be provided to the physicians for dissemination, we also recommend that the display stand at each physician's office include at least 100 copies of the Dear Consumer letter and be available for at least 90 days. We further recommend that your sales force monitor the display stands to ensure that sufficient copies of the Dear Consumer letters are available for the entire duration of the 90-day corrective period.

Dear Healthcare Professional (DHP) Letter

We reviewed your revised DHP letter and have no further comments at this time.

Dear Consumer Letter

We reviewed your revised Dear Consumer letter and offer the following underlined revisions on page three. Deletions are noted with a strikethrough.

- "Do not stop taking Kadian or any other opioid without talking to your healthcare professional. Kadian can cause physical dependence. ~~Do not stop taking Kadian or any other opioid without talking to your healthcare professional.~~ This means you could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. . ."

Envelope

We reviewed your proposed envelope that will accompany the DHP and Dear Consumer letters and offer the following comment:

- Please revise or clarify the company name currently listed in the return address field: "Actavis Kadian LLC." (emphasis added)

Please submit a written response to this letter on or before May 3, 2010. The response should include a revised dissemination plan, finalized DHP letter, revised Dear Consumer letter, and revised envelope.

Please direct your response to me at the 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, facsimile at (301) 847-8444.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20616	ORIG-1	ACTAVIS ELIZABETH LLC	KADIAN (MORPHINE SULFATE) ER CAPS 20/50

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELAINE H CUNNINGHAM
04/19/2010

actavis
creating value in pharmaceuticals

Confidential -- Not For Public Disclosure

May 3, 2010

VIA OVERNIGHT MAIL DELIVERY

Thomas Abrams, RPh, MBA
Director
Division of Drug Marketing, Advertising, and Communications
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 20-616
Kadian® (morphine sulfate extended-release) Capsules, CII
MACMIS #18148

Dear Mr. Abrams,

Reference is made to the Division of Drug Marketing, Advertising, and Communication's (DDMAC) April 19, 2010 letter regarding Actavis Elizabeth LLC's ("Actavis") April 9, 2010 response that provided clarification and revisions to its proposed dissemination plan. Further reference is made to the February 18, 2010 DDMAC Warning Letter for Kadian® (morphine extended-release) Capsules, CII ("Kadian"), Actavis' March 4, 2010 initial response, and DDMAC's subsequent March 26, 2010 letter requesting clarifications and revisions.

DDMAC's April 19, 2010 letter requests that Actavis respond with a revised dissemination plan, a finalized Dear Healthcare Professional Letter ("DHP Letter"), a revised Dear Consumer letter, and a revised envelope. As requested, Actavis is providing the following response.

Revised Dissemination Plan

Actavis originally proposed to distribute the Dear Consumer letters to physician offices based upon the number of patients per office that used a Co-Pay Assistance Card. The number of letters ranged from four letters to physicians with two or fewer patients who used the Co-Pay Assistance Card to 110 letters to physicians with 50 or more patients who used the card. According to DDMAC, this proposal may not necessarily reach all of the patients who could have been exposed to the Co-Pay Assistance Program Brochure and/or Co-Pay Assistance Card.

Instead, DDMAC recommended that in addition to the copies provided to the physicians for dissemination, Actavis should provide a display stand at each physician's office that includes at least 100 copies of the Dear Consumer letter for at least 90 days. It further recommended that

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

Actavis' sales force monitor the display stands to ensure that sufficient copies of the Dear Consumer letter are available for the entire duration of the 90-day corrective period.

Actavis acknowledges DDMAC's concerns regarding the proposed dissemination plan. To that end, Actavis proposes to disseminate 100 Dear Consumer letters to each physician's office. It further proposes to send a separate letter to each physician with instructions for disseminating the letter to the patient and displaying the remaining letters in the waiting room. A draft of this proposed "instructional" letter is provided in Attachment 1. Please note that under this plan, Actavis will instruct the physician to pull the number of letters he or she requires for direct dissemination to his or her patients from the packet of 100 letters provided with the display stand.

To ensure that sufficient copies of the Dear Consumer letters are available in each physician's office during the 90-day period, Actavis proposes the following:

- Actavis' sales force will check that the letters are properly displayed and stocked in those offices that they physically visit.

- For offices that do not receive a visit, Actavis will call the office to inquire if the package was received and whether additional copies of the letters are needed for the display stand. Actavis proposes to make one call, a month, per office.

- Finally, the "instructional" letter to each physician will provide a 1-800 number so that the physician can obtain additional copies of the Dear Consumer letter.

Actavis believes this is a reasonable approach based on the size of Actavis' sales force (18 individuals) and the number of physician offices they call on (approximately 1450). The cumulative effort of actual office visits, phone calls to physician office, and the 1-800 number to obtain additional letters will ensure the necessary reach to affected consumers.

Revised Dear Consumer Letter

Provided in Attachment 2 is the revised Dear Consumer letter incorporating DDMAC's revisions.

Envelope

The envelope bears the return address of Actavis Kadian LLC because that entity is the exclusive distributor of the Kadian product. The product label, package insert, and promotional materials all refer to Actavis Kadian LLC. The manufacturer and NDA holder of Kadian is Actavis Elizabeth LLC. Actavis US encompasses all of the Actavis entities in the United States. For that reason, Actavis is proposing to maintain the envelope with Actavis Kadian LLC as the return addressee. For consistency, Actavis has revised its Dear Consumer to read: "You are receiving this letter because you may have received from Actavis Kadian LLC ("Actavis") a Co-Pay Assistance Program Card which was attached to a Co-Pay Assistance Program Brochure." Similarly, Actavis has revised its DHP letter to read: "Between March 2009 and December 2010,

NDA 20-616
Kadian® (morphine sulfate extended-release) Capsules, CII
MACMIS #18148

Actavis Kadian LLC ("Actavis") sales representatives, during office visits with physicians, distributed a certain material to promote Kadian...." Attachment 3 contains the finalized DHP letter enclosed in the envelope.

Actavis appreciates DDMAC's comments and suggestions for improving Actavis' corrective messages. Actavis trusts that you will find that the revised dissemination plan and letters address all issues raised in the April 19, 2010 DDMAC response.

Please do not hesitate to contact me at 908-659-2317 if you have questions.

Sincerely,

Terri Nataline
Vice President, Regulatory and Medical Affairs
Actavis US

Enclosures

cc: Elaine Hu Cunningham, Pharm. D., Senior Regulatory Review Officer
CDER, DDMAC Communications
(via facsimile: 301-847-8444)

Doug Boothe
Chief Executive Officer
Actavis US

ATTACHMENT 1

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May __, 2010

VIA FIRST CLASS MAIL

[Insert Physician Name & Address]

Re: Kadian® (morphine sulfate extended-release) Capsules, CII

Dear Healthcare Professional,

In conjunction with the letter we recently sent regarding the important information for Kadian Capsules, and in an effort to ensure that patients are fully informed, please find enclosed 100 copies of our Dear Consumer letter. These letters contain important patient information and should be given to all patients taking Kadian. Please display the remaining letters in your waiting area in the enclosed stand.

Actavis made a commitment to the Division of Drug Marketing, Advertising, and Communications ("DDMAC") to make this important corrective drug information regarding Kadian available to patients for a 90-day period. We request that you put this display stand and letters in your waiting area so that all patients have ready access to the information contained in the letter. We will be contacting the office monthly to ensure that you have sufficient copies of the letter available for your patients during the 90-day period. If you need additional copies of the letter in the interim, please contact an Actavis representative at 1-877-637-4629.

Sincerely,

Doug Boothe
Chief Executive Officer
Actavis US

CONFIDENTIAL DRAFT
FOR REVIEW PURPOSES ONLY

Actavis, Inc. | 60 Columbia Rd., Bldg. B Morristown, NJ 07960 | t (973) 993-4501 | www.actavis.com

ATTACHMENT 2

actavis
creating value in pharmaceuticals

IMPORTANT:
Correction of Drug Information about
KADIAN® (morphine sulfate extended-release) Capsules, CII

May__, 2010

Dear Valued Consumer,

You are receiving this letter because you may have received from Actavis Kadian LLC ("Actavis") a Co-Pay Assistance Program Card which was attached to a Co-Pay Assistance Program Brochure. This letter specifically concerns the Co-Pay Assistance Program Brochure ("Brochure"), which was the subject of a Warning Letter issued by the U.S. Food and Drug Administration ("FDA") on February 18, 2010.

In the Warning Letter, FDA raised the following concerns about the Brochure: (1) it left out and minimized serious risks associated with Kadian; (2) it claimed Kadian was approved by FDA for conditions it is not approved for; and (3) it presented unsupported claims about how well it works.

Actavis would like to take the opportunity to correct and clarify the statements and representations about Kadian made in the Brochure.

I. Indication

FDA objected to the general discussion in the Brochure regarding "chronic pain" and "pain management," stating that this discussion suggested that Kadian is appropriate to treat all types of chronic pain.

Please note that Kadian is indicated to treat only certain types of pain. Specifically:

> KADIAN® capsules are an extended-release capsule taken by mouth of morphine sulfate that is used to manage moderate to severe pain that continues around-the-clock and is expected to last for an extended period of time.
>
> **KADIAN® is NOT for use to treat pain that occurs once in a while ("as needed").**
>
> KADIAN® is not indicated for pain in the immediate post-operative period (12-24 hours following surgery) for patients who have not taken drugs called opioids before.
>
> KADIAN® is not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

Please remember to consider the above information about the appropriate use of Kadian, including its limitations on use, and discuss these issues with your doctor.

II. Risks

FDA stated that while the Brochure mentioned certain risks associated with Kadian (including information on its boxed warning (see below)), the Brochure failed to include other important and serious risk information. Moreover, FDA objected to the Brochure's use of medical language to explain these risks to patients because such information may not be easily understood.

Please see below a discussion of the most important and serious risks associated with Kadian, and please refer to the enclosed full Prescribing Information for additional discussion of these risks.

A. In The FDA Approved Prescribing Information for Healthcare Providers:

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.

B. What This Means for You:

Most Important Information to Know About Kadian

- Kadian, which is a federally controlled substance (CII), can be abused by people who abuse prescription medicines or street drugs. To prevent theft, misuse, or abuse of KADIAN®, keep it in a safe place. Do not give Kadian to anyone else. It may harm them or even cause death. After you stop taking Kadian, flush any unused capsules down the toilet.

- Do not crush, dissolve, or chew Kadian capsules or the capsule contents before swallowing. Abuse of Kadian by crushing, chewing, snorting or injecting the dissolved product will result in the uncontrolled delivery of morphine and pose a significant risk to the abuser that could result in overdose or death.

- KADIAN® is **NOT** for use to treat pain that occurs once in a while ("as needed").

- Kadian 100 mg and 200 mg capsules are for use only in opioid tolerant patients. "Opioid tolerant" means that you regularly use another opioid medicine for constant pain and that your body is used to it. **Ingesting Kadian 100 mg and 200 mg capsules when you are not opioid tolerant may cause serious breathing problems and death.**

Do Not Take Kadian If:

- You have a known hypersensitivity (allergy) to morphine, morphine salts, or any of the ingredients in Kadian (See the accompanying Prescribing Information for a complete list of ingredients in Kadian).

- You are having an asthma attack or have severe asthma, trouble breathing, or lung problems.

- You have a bowel blockage called paralytic ileus.

- Do not take Kadian with alcohol, other opioids, or illicit drugs because dangerous additive effects may occur resulting in serious injury or death. In addition, alcohol can cause very high levels of morphine in your blood and you can die due to an overdose of morphine.

Possible Side Effects of Kadian

- Kadian can cause serious breathing problems that may be life-threatening, especially if Kadian is used in the wrong way. Call your healthcare professional or get medical help right away if your breathing slows down, you have shallow breathing, you feel faint, dizzy, confused, or have any unusual symptoms. These can be symptoms that you have taken too much Kadian or that the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

- Do not stop taking Kadian or any other opioid without talking to your healthcare professional. Kadian can cause physical dependence. This means you could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addition. Your doctor can tell you more about the differences between physical dependence and drug addiction.

- There is a chance of abuse or addiction with Kadian.

- Serious allergic reactions, while extremely rare, have been reported with use of Kadian. Get medical help right away if you experience any symptoms of a severe allergic reactions, such as: feeling dizzy or faint, trouble breathing, chest pain, or swelling of the face, throat, or tongue.

- Do not drive or operate machinery or perform other potentially hazardous activities until you know how you react to this medicine or a change in the dose.

Please Remember

- These are not all the risks and side effects associated with Kadian. For more information, please contact your doctor.

- Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

III. Unsubstantiated Effectiveness Claims

FDA objected to the following statements in the Brochure regarding chronic pain:

- ". . . Many Americans suffer from chronic or ongoing pain. It can cause you to miss work and can even keep you from enjoying life. If left untreated, pain can place stress on your body and your mental health . . . ."

- " . . . Chronic pain . . . can be inconvenient and can keep you from your daily tasks."

FDA stated that the above representations suggested that use of Kadian results in a positive impact on a patient's work, physical and mental functioning, daily activities, or enjoyment of life. FDA stated that these representations were misleading because they suggested that Kadian is more effective than has been demonstrated. FDA is not aware of any evidence demonstrating that Kadian treatment results in a positive impact in these areas.

******

Please see the enclosed full Prescribing Information for Kadian. If you have any questions regarding Kadian or this letter, please consult with your doctor or call 1-877-637-4629.

Sincerely,

Doug Boothe
Chief Executive Officer
Actavis US

ATTACHMENT 3

IMPORTANT
CORRECTION
OF DRUG
INFORMATION
Actavis Kadian LLC
60 Columbia Road, Bldg. B
Morristown NJ 07960 USA

actavis
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Fax message

To	Elaine Hu Cunningham, Pharm. D., Senior Regulatory Review Officer		
Date	05/03/2010	Fax No	301-847-8444
No of pages (including this one)	12		
Subject	MACMIS #18148		
From	Terri Nataline, Vice President, Regulatory and Medical Affairs		

********** -COMM. JOURNAL- ********** DATE MAY-03-2010 ***** TIME 03:46 *********

MODE = MEMORY TRANSMISSION START=MAY-03 03:44 END=MAY-03 03:46

FILE NO.=724

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	913018478444	013/013	00:01:46

-ACTAVIS -

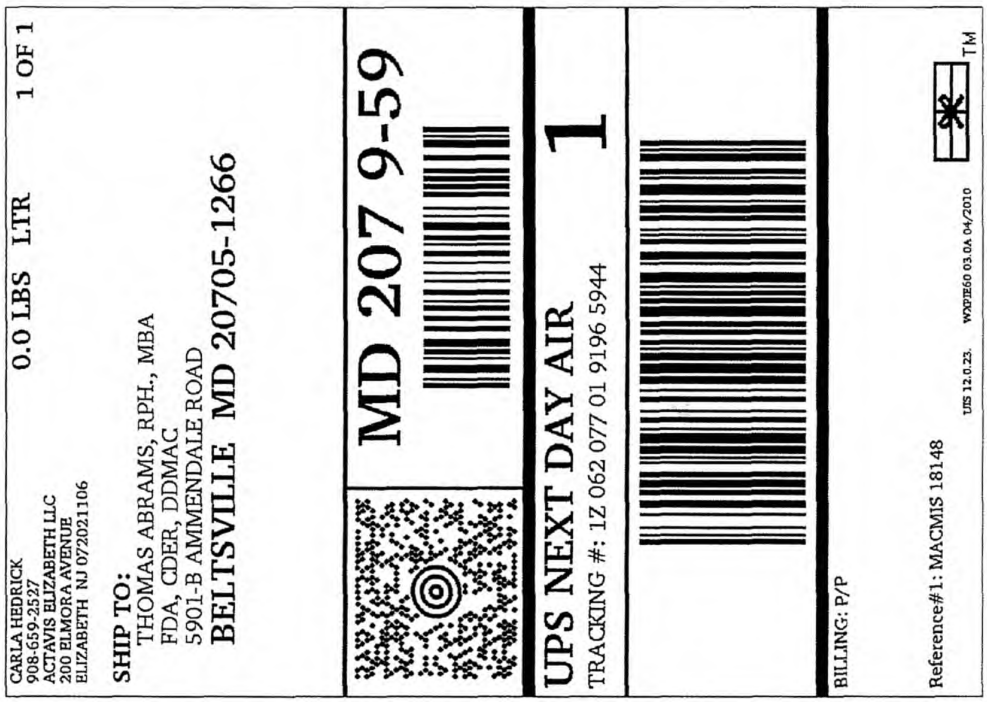
********** -REGULATORY AFF - ***** - 908 659 2250- **********

actavis
creating value in pharmaceuticals

Fax message

To	Elaine Hu Cunningham, Pharm. D., Senior Regulatory Review Officer		
Date	05/03/2010	Fax No	301-847-8444
No of pages (including this one)	12		
Subject	MACMIS #18148		
From	Terri Nataline, Vice President, Regulatory and Medical Affairs		

PLEASE REFER TO THE ACTUAL SAMPLE OF THE ENVELOPE AND CONSUMER LETTER BEING SENT VIA OVERNIGHT MAIL

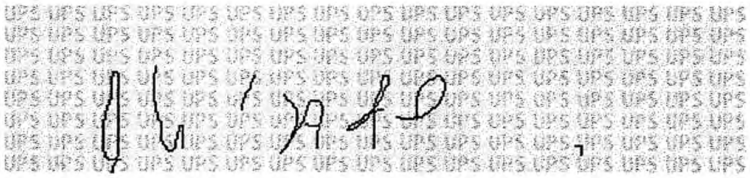


Proof of Delivery

Dear Customer,

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

Tracking Number:	1Z0620770191965944
Reference Number(s):	MACMIS 18148
Service:	NEXT DAY AIR
Shipped/Billed On:	05/03/2010
Delivered On:	05/04/2010 9:13 A.M.
Delivered To:	5901B AMMENDALE RD BELTSVILLE, MD, US 20705
Signed By:	WADE



Location:	RECEIVER

Thank you for giving us this opportunity to serve you.

Sincerely,

UPS

Tracking results provided by UPS: 05/05/2010 8:57 A.M. ET

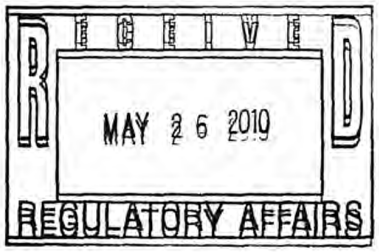
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Terri Nataline
Vice President, Regulatory and Medical Affairs
Actavis US
60 Columbia Road, Building B
Morristown, NJ 07960



RE: NDA 020616
Kadian® (morphine extended-release) Capsules, CII
MACMIS #18148

Dear Ms. Nataline:

This letter responds to Actavis Elizabeth LLC's (Actavis) May 3, 2010, letter submitted to the Division of Drug Marketing, Advertising, and Communications (DDMAC) in response to DDMAC's April 19, 2010, letter requesting clarification and revisions to Actavis' April 9, 2010, proposed dissemination plan, Dear Healthcare Professional (DHP) letter, and Dear Consumer letter. Reference is made to the February 18, 2010, DDMAC Warning Letter for Kadian® (morphine extended-release) Capsules, CII (Kadian), Actavis' initial response dated March 4, 2010, and DDMAC's subsequent March 26, 2010, letter.

DDMAC has reviewed your revised dissemination plan and revised proposed corrective letters and we acknowledge that Actavis is working towards correcting the issues cited in the Warning Letter. However, DDMAC finds that the proposed revised dissemination plan for the Dear Consumer letter does not adequately address our request for Actavis to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed the Warning letter to the audiences that received the violative promotional materials. In the interest of time, we have included a revised dissemination plan for the Dear Consumer letter that we feel adequately addresses this request.

Dissemination Plan

Your proposal to disseminate the Dear Consumer letters and instructional letter to physicians' offices that do not receive a visit from a representative of your sales force is not adequate to ensure that the Dear Consumer letters will be properly displayed for the duration of the 90-day corrective period.

Therefore, DDMAC recommends the following dissemination plan:

- Corrective messaging display stands will be placed in each of the approximately 1,450 physicians' offices for 90 days with at least 100 copies of the Dear Consumer letter.

- Actavis representatives will physically visit each physician's office to set up and stock each display stand and will provide each physician with an adequate supply of Dear Consumer letters for direct dissemination to their patients who are taking Kadian.

- Actavis representatives will follow-up with each physician's office via monthly telephone calls during the 90 day corrective period to ensure that sufficient copies of the Dear Consumer letters are available after the initial visit.

We acknowledge your explanation regarding the size of your sales force in relation to the number of offices that need to be reached and therefore request that you submit a proposed reasonable timetable for each physician's office to be physically visited by a representative of your sales force.

We recommend that you submit a revised dissemination plan for the Dear Consumer letters as described above. Based on the proposed plan described above, we do not recommend dissemination of a separate "Instructional" letter to physicians regarding this matter.

Dear Healthcare Professional (DHP) Letter, Dear Consumer Letter, and Envelope

We appreciate your revisions and clarifications regarding the DHP letter, Dear Consumer letter, and envelope and have no further comments at this time.

We remind you that the approved product labeling should accompany the DHP and Dear Consumer letters and the mailings should be done in accordance with 21 CFR 200.5, "Important Correction of Drug Information."

Please submit final copies of the DHP and Dear Consumer letters and envelope on Form FDA-2253 at the time of initial dissemination and submit a written confirmation to DDMAC once dissemination of the DHP and Dear Consumer letters has been completed.

Please submit a written response to this letter on or before May 27, 2010. The response should include a revised dissemination plan of the Dear Consumer letters to physicians' offices.

Please direct your response to me at the 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, facsimile at (301) 847-8444.
In all future correspondence regarding this matter, please refer to MACMIS #18148 in addition to the NDA number.

We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

Sincerely,

{See appended electronic signature page}

Elaine Hu Cunningham, Pharm.D.
LCDR, United States Public Health Service
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20616	ORIG-1	ACTAVIS ELIZABETH LLC	KADIAN (MORPHINE SULFATE) ER CAPS 20/50

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELAINE H CUNNINGHAM
05/20/2010

actavis

FILE COPY

Confidential -- Not For Public Disclosure

June 10, 2010

VIA OVERNIGHT MAIL DELIVERY

Thomas Abrams, RPh, MBA
Director
Division of Drug Marketing, Advertising, and Communications
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 20-616
Kadian® (morphine sulfate extended-release) Capsules, CII
MACMIS #18148

Dear Mr. Abrams,

Reference is made to the Division of Drug Marketing, Advertising, and Communication's (DDMAC) May 20, 2010 letter in response to Actavis Elizabeth LLC's May 3, 2010 submission clarifying its proposed dissemination plan. Further reference is made to the February 18, 2010 DDMAC Warning Letter for Kadian® (morphine extended-release) Capsules, CII ("Kadian").

In its May 20, 2010 letter, DDMAC stated that Actavis' proposed dissemination plan did not adequately address the dissemination of the corrective messages to the consumer audiences that received the violative materials. Accordingly, Actavis is proposing a revised Dear Consumer letter and a revised dissemination plan for its letter. This revised plan also clarifies a number of issues that had not been previously resolved in Actavis' earlier communications with DDMAC.

As stated in its March 4, 2010 response, Actavis distributed approximately 170,000 Co-Pay Assistance Program Brochures. Consumers have received these brochures (1) in response to telephone requests, (2) through on-line web site requests, and (3) through healthcare professional's offices and retail pharmacies. As a corrective measure, Actavis proposed to mail the Dear Consumer letter to each consumer who received a Co-Pay Assistance Program Card directly from Actavis, regardless of whether the patient redeemed the card. This portion of the proposed dissemination plan remains unchanged.

To reach consumers who may have received the Co-Pay Assistance Program Brochure through their healthcare professionals, Actavis proposed to distribute a certain number of Dear Consumer letters to each healthcare professional's office based on the number of patients per healthcare professional that redeemed a co-pay card. (*See* Actavis' April 9, 2010 Ltr, p 3). Therefore, Actavis' prior proposed plan limited the scope of dissemination because it equated evidence of

200 Elmora Avenue
Elizabeth, NJ 07207
908 527 9100
908 659 2250
www.actavis.com

co-pay card use with consumer exposure to the Co-Pay Assistance Program Brochure. This plan would not reach consumers that may have received the Co-Pay Assistance Program Brochure through their healthcare professionals but never used the co-pay card.

Therefore, Actavis now proposes to expand the original plan's scope by disseminating the Dear Consumer letter to all healthcare professionals' offices that received the Co-Pay Assistance Program Brochure, regardless of whether patients from that office redeemed the co-pay cards or not.

I. Revised Dissemination Plan for Dear Consumer Letter

There were a total of approximately 10,000 healthcare professionals' offices and 558 pharmacies that received the Co-Pay Assistance Program Brochure. Actavis proposes to physically visit each of these offices and pharmacies and set up a stand in the waiting room or area with 25 copies of the Dear Consumer letter. An Actavis representative will follow-up with a monthly telephone call or physical visit to each healthcare professional's office during the 90-day corrective period to ensure that sufficient copies of the Dear Consumer letters remain available after the initial visit. Should more copies be needed, Actavis will mail replacement copies to the office. Finally, Actavis will provide a phone number for the healthcare professional's offices to call in the event that they need additional copies of the letter.

To perform these activities, Actavis intends to temporarily increase its sales force from its existing 18 sales representatives to 40 to 50 sales representatives. The proposed time frame for completing the visits to each healthcare professional's office or retail pharmacy is approximately eight weeks. This time frame assumes about five office and/or pharmacy visits per day, per sales representative, depending on the geographic location of each office. The time table will begin following the training of the existing sales force and the temporary sales force. This training will occur as soon as possible after reaching agreement with DDMAC on the final dissemination plan. At that time, Actavis will provide DDMAC with the exact date of the sales force training meeting and the subsequent roll-out of the dissemination plan.

II. Revised Dissemination Plan for the Dear Healthcare Professional Letter

Actavis originally proposed to send the corrective Dear Healthcare Professional (HCP) letter to the 1900 healthcare professionals identified in its database of target healthcare professionals for its sales force. These are the healthcare professionals who received the Comparison Detailer. Actavis is now proposing to broaden the dissemination of the Dear HCP letter to an audience not previously identified in its correspondence with DDMAC.

Regrettably, Actavis recently discovered information regarding certain promotional activities conducted by its telemarketing team. That team was hired shortly after Actavis acquired the KADIAN® NDA from Alpharma, Inc. The team was responsible for calling healthcare professionals to inform them of Actavis' intent to continue offering the Co-Pay Assistance Program initiated by Alpharma. In doing so, the telemarketing team followed a script that recites information similar in content to that found in the objectionable Comparison Detailer. The script's content was brought to the attention of Actavis' legal and regulatory teams for the first

time subsequent to FDA's May 20, 2010 letter. Upon its discovery, Actavis immediately ordered the telemarketing team to cease all activities.

A copy of the script used by the telemarketing team is provided in Attachment 1. The script is also being submitted on Form 2253 under separate cover. Actavis acknowledges that this script should have been submitted to DDMAC upon first use as required under the Post-Marketing Reporting Requirements set forth in 21 CFR 314.81(b)(3). Actavis is taking the necessary corrective actions to ensure that proper procedures for the review and submission of promotional materials are followed in the future.

To address the external exposure to the objectionable script, Actavis proposes to broaden the dissemination of its Dear HCP letter by sending it to the healthcare professionals' offices that were the subject of a completed call from a telemarketing representative. A "completed call" means that a telemarketing representative was able to speak to someone at the healthcare professional's office (nurse, receptionist, healthcare professional, etc.).

Since its inception, the telemarketing team made 6,200 completed calls to healthcare professionals. In addition, 1900 healthcare professionals received a Comparison Detailer from a sales representative. However, some healthcare professionals received both a telemarketing call and information from our sales representatives. Thus, the total number of healthcare professionals exposed to either a completed call or the Comparison Detailer is between 6,200 and 8,100. We are working to determine the final number of healthcare professionals by removing any duplication.

III. Revised Corrective Letters

A. Revised Dear Consumer Letter

After further review of the Dear Consumer letter, Actavis has decided to revise the text so that the corrective message is presented in a more consumer-friendly manner. This revised letter provides truthful, non-misleading, and complete corrective messages about the issues raised in the warning letter. It does not republish the promotional statements DDMAC found objectionable and does not describes the risks associated with the use of Kadian in the "highly complex, medical technical language" DDMAC criticized.

In light of the important health message it delivers to KADIAN® patients, the instruction to patients not to discontinue KADIAN® without first talking to their HCP was moved to the introduction section of the Consumer Letter. In the previous version of the Consumer Letter that DDMAC determined was acceptable, this information appeared on page three under side effects and is based on information in the "Information for Patients" and "Cessation of Therapy" sections of the labeling.

The proposed revised letter clearly corrects the statements and representations previously made in the Co-Pay Assistance Program Brochure in plain English and does not overwhelm the consumer with complex and duplicative information. The revised Dear Consumer letter is provided in Attachment 2.

B. Revised Dear Healthcare Professional Letter

Actavis has revised the introduction section of the Dear HCP letter to address healthcare professionals who answered a call from Actavis telemarketing representatives in addition to the healthcare professionals who received the Comparison Detailer and similar promotional materials. In addition, we revised Section III B. of the letter to delete, and thus avoid a republication of, the objected to claims. The revised Dear HCP letter is provided in Attachment 3.

IV. Conclusion

It is important to emphasize that Actavis takes very seriously the issues raised in the DDMAC Warning Letter and is committed to resolving all outstanding issues in an expedient and complete manner. Actavis had previously proposed a plan which was based on the facts then available and believed in good faith that the plan adequately addressed all of the issued raised in the Warning Letter. Regrettably that plan reflected some inexperience in addressing DDMAC-related matters. This combined with the discovery of new facts regarding its earlier promotional campaign necessitated the revisions provided in this response. Actavis is confident it now has all relevant facts as to the dissemination of all materials and content to which DDMAC objects.

Actavis trusts that the expanded dissemination plan and revised corrective letters now address DDMAC's request for Actavis to disseminate truthful, non-misleading, and complete corrective messages about the issues raised in the Warning Letter.

Sincerely,

Terri Nataline
Vice President, Regulatory and Medical Affairs
Actavis US

Enclosures

cc: Elaine Hu Cunningham, Pharm. D., Senior Regulatory Review Officer
CDER, DDMAC Communications
(via facsimile: 301-847-8444)

Doug Boothe
Chief Executive Officer
Actavis US

John LaRocca
Chief Legal Officer
Actavis US

ATTACHMENT 1

REVISED: TMS Health Telesales Script

October 22, 2009

Call Introduction:

Gatekeeper Opening

Good morning/afternoon. This is _____. I am calling on behalf of Actavis Pharmaceuticals. May I ask to whom I am speaking? **(Record the name of the Gatekeeper)**. I would like to speak with Dr _____regarding Kadian Extended Release Capsules. Kadian is used in the treatment of patients with moderate to severe chronic pain. I am sure Dr._____is familiar with Kadian. Actavis has also re-initiated the discount prescription coupon program that may be very helpful to your patients. (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 new co-pay assistance card program. 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 Pharmaceuticals. 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 Extended Release Capsules. I am sure Dr._____is familiar with Kadian. Actavis has re-initiated the co-pay assistance card 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 updated information about Kadian and the opportunity to discuss several 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 Pharmaceuticals regarding **Kadian Extended Release Capsules**. As you know, Kadian (Morphine Sulfate) Extended Release Capsules 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.

I wanted to let you know that Kadian Extended Release Capsules are still available for your patients.

You might be interested in learning that Actavis has re-initiated the **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.

What do you currently use to treat your patients with chronic pain?

What do you like about (SPECIFIC PRODUCT MENTIONED BY MD)?

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

GO TO SHEET WITH SPECIFICS CONCERNING Avinza, Opana ER, Embeda

As you may recall:

- Kadian is safe and effective

- Kadian provides the convenience of once or twice daily dosing and can provides smooth and steady blood levels for your pain patients.

- Kadian provides you more dosing flexibility when prescribing a long-acting morphine.

-Kadian is available in 8 different strengths and can be titrated in 10mg increments.

-Kadian contains no ceiling dose, does not contain acetaminophen

-Kadian has 3 modes of administration – capsules, sprinkle option or G-tube dosing

-Kadian has no significant food effect

Actavis will continue to support your patients with our co-pay assistance card program as well as the 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 doctor uses co-pay cards/ Would you like to receive additional co-pay assistance cards?

FAIR BALANCE

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 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 CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES TO BE 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.
Serious adverse reactions that may be associated with KADIAN® therapy in clinical use are those observed with other opioid analgesics and include: respiratory depression, respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock.

Please consult the full prescribing information we will be sending you for more information.

CLOSE

Based on the information I provided you Dr. _____, would you prescribe **Kadian Capsules** for appropriate patients? **(Record Answer)**

Dr. _____, would you be interested in receiving discount coupons 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 Pharmaceuticals and myself, thank you for your time. If you have any further questions please feel free to contact us at 1-XXX-XXX-XXXX.

Highlights of Kadian® vs. competition

Kadian® advantages over EMBEDA ™

- KADIAN has a long history of safety and efficacy
- Known and trusted side effect profile
- KADIAN has excellent managed care coverage with most plans at second or third tier
- $50 co-pay card reduces the out-of-pocket expenses significantly
  - Can be used 2x per month and 12 times total
- KADIAN is stocked in pharmacies nationwide

Kadian® advantages over OPANA ER™

- Kadian has flexibility of dosing once or twice a day
- No food effect. Can be administered with or without food for dosing convenience
- Kadian is morphine with a long history of safety and efficacy
- Known and trusted side effect profile
- Kadian can be titrated in 10 mg increments
  - 10 mg of Kadian is the lowest dose of morphine or morphine equivalent available; especially useful for the elderly
- Kadian has a more generous co-pay assistance program ($50 vs. $25)
- Kadian is preferred on more state public aid programs
- Kadian is placed on more tier 2 formularies than Opana ER
- Kadian can be titrated up more rapidly which is important for new patients; every other day vs. Opana ER which is every 3 to 7 days
- More dosing options than oxymorphone
  - Eight capsule strengths of KADIAN
  - Sprinkle option
  - G-tube option

Kadian® advantages over AVINZA®

- Coupon program
  - Up to $50 off each prescription of Kadian and can be used twice per month (up to 12 times.)
- Better Managed Care Coverage – more plans covering Kadian at Tier 2 and Tier 3
- Kadian has a smooth PK curve with fewer peaks and valleys
- Kadian has flexibility of dosing once or twice a day. Avinza can only be dosed q24h.
  - The twice daily dosing can be done asymmetrical.
- Kadian's 10mg strength provides flexibility to the physician to start patients at a lower dose than Avinza's lowest strength of 30mg
  - Especially important with elderly and conversions from IR opioids.
- Kadian can be titrated in 10 mg increments – same as above.
- Avinza contains an immediate-release component that peaks in 0.5hr. This mimics short acting medications. Short acting medications should be reserved for PRN use. In addition, there is a trend towards eliminating short acting medications in chronic pain treatment
- The dose of Avinza is limited to a maximum dose of 1600mg per day due to potential renal toxicity from the fumaric acid component. Kadian does not contain fumaric acid

For training purposes only. Not to be distributed.

- More dosing options than Avinza
  - Eight capsule strengths of KADIAN
  - G-tube option

Kadian® advantages over MS Contin®

- Fewer Peak and Valleys
  - Smooth steady-state plasma levels compared with controlled-release (CR) morphine tablets at q12h and q24h.
- Better Pain Control and Improved Sleep scores vs. CR morphine tablets
  - 36% Improvement in pain score
  - 47% improvement in sleep score
- Fewer Barriers to prescribing
  - 8 strengths for Kadian® vs. MS Contin
  - Excellent reimbursement – primarily tier 2 and tier 3
  - $50 dollar co-pay assistance program
    - Average co-pay across the country is $40.00
    - Can be used up to 2 times per month
    - 12 times in a year
- Kadian 10-mg and 20-mg formulations allow a physician to begin therapy at a lower dose than the 30-mg lowest strength of MS Contin.
- Kadian allows dose titration at lower doses in 10-mg increments
- MS Contin is dosed primarily Q8h. Kadian can be dosed q12h or q24 in clinical practice.
- Kadian provides steady and consistent blood plasma concentrations with less Fluctuation than MS Contin
- KADIAN is approved for sprinkle and G-tube administration. MS Contin tablet technology does not allow this type of administration.

ATTACHMENT 2

actavis
creating value in pharmaceuticals

IMPORTANT:
Correction of Drug Information about
KADIAN® (morphine sulfate extended-release) Capsules, Schedule II

June ___, 2010

Dear Valued Consumer,

You are receiving this letter because you may have received from Actavis a Co-Pay Assistance Program Card which was attached to a Co-Pay Assistance Program Brochure. This letter specifically concerns the Co-Pay Assistance Program Brochure ("Brochure"), which was the subject of a Warning Letter issued by the U.S. Food and Drug Administration ("FDA") on February 18, 2010.

In the Warning Letter, the FDA raised the following concerns about some of the information in the Brochure. Specifically, the FDA was concerned that the brochure (1) left out or minimized serious risks associated with KADIAN®; (2) suggested that KADIAN® was approved by the FDA for conditions for which it was not approved; and (3) presented or suggested unsupported claims about how well KADIAN® works.

This letter clarifies and corrects the information about KADIAN® presented in the Brochure.

Do NOT stop taking KADIAN® without talking to your doctor. KADIAN®, like any opioids, can cause physical dependence. You could become sick with uncomfortable withdrawal symptoms because your body has become used to it. Physical dependence is not the same as drug addition.

What are the approved uses for KADIAN®?

KADIAN® is a prescription medicine containing morphine sulfate that is taken by mouth. It is an extended-release formulation that is used for the management of moderate to severe pain when continuous, around-the-clock pain relief is needed for a long period of time.

- **KADIAN® is NOT for use to treat pain that occurs once in a while ("as needed").**
- KADIAN® **is NOT** indicated for pain in the immediate post-operative period (12-24 hours following surgery) or if the pain is mild or not expected to last for a long time.
- KADIAN® **IS** indicated for post-operative use if the patient was already taking it prior to surgery, or if the post-operative pain is expected to be moderate to severe and last a long time.

Actavis Inc | 60 Columbia Rd., Bldg. B Morristown, NJ 07960 | (973) 993-4501 | www.actavis.com

Who should not take KADIAN®?

Do NOT take KADIAN® if:

- you have a known hypersensitivity (allergy) to morphine, morphine salts, or any of the ingredients in KADIAN® (See the accompanying Product Information for a complete list of ingredients in KADIAN®);
- in any situation where narcotic medication should not be used;
- you are having an asthma attack or have severe asthma, trouble breathing, or lung problems; or
- you have a type of bowel blockage called paralytic ileus.

What Other Important Information Should You Know?

- **KADIAN® contains morphine sulfate, which is a Schedule II controlled substance that can be abused by people who abuse prescription medicines or street drugs.**
- **KADIAN®100 mg and 200 mg capsules are for use only in opioid tolerant patients. Taking KADIAN® 100 mg and 200 mg capsules when you are not opioid tolerant may cause serious breathing problems and death.** "Opioid tolerant" means that you regularly use another opioid medicine for constant (around the clock) pain and that your body is used to it.
- To prevent theft, misuse, or abuse of KADIAN®, keep it in a safe place. Keep KADIAN® out of reach of children.
- Do not give your KADIAN® to anyone else – inappropriate use may harm them or even cause death. After you stop taking KADIAN®, flush any unused capsules down the toilet.

How do I take KADIAN®?

- Take KADIAN® exactly as prescribed by your doctor.
- **KADIAN® Capsules should be swallowed whole. Do not crush, dissolve, or chew KADIAN® capsules or the pellets in the capsules before swallowing due to the risk of rapid release and absorption of a potentially fatal dose of morphine.**
- KADIAN also may be taken by opening the capsules and sprinkling the entire contents on a small amount of cool or room temperature applesauce. **Do not chew the pellets.** Do not drive or operate machinery or perform other potentially hazardous activities until you know how you react to KADIAN® or a change in your KADIAN® dose.
- Do not take KADIAN® with alcohol, other opioids, or illicit drugs because dangerous additive effects may occur resulting in serious injury or death. Tell your health care

provider about all of your medical conditions and all of the medications and supplements you are taking.

What Are the Possible Side Effects of KADIAN®?

- Serious adverse reactions that may be associated with KADIAN® include difficulty breathing, circulatory depression, cardiac arrest, low blood pressure and shock. Breathing problems are the chief hazard of all morphine products and occur more often in elderly and debilitated patients and those with other medical conditions that affect breathing.
- The most frequent side effects include drowsiness, dizziness, constipation and nausea.
- Severe constipation is a common side effect of opioids, including KADIAN®; talk to your doctor about appropriate laxatives, stool softeners and other treatments.
- There is a chance of physical dependence, abuse or addiction with KADIAN®.
- Call your doctor for medical advice about side effects. In addition, you may report side effects to FDA at 1-800-FDA-1088.
- These are not all the risks and side effects associated with KADIAN®. For more information, please contact your doctor.

Unsubstantiated Effectiveness Claims

FDA was concerned that statements in the brochure suggested that the use of KADIAN® could result in a positive impact on a patient's work, physical and mental functioning, daily activities, or enjoyment of life. In FDA's view, these representations were misleading because they suggested that KADIAN® is more effective than has been demonstrated. FDA is not aware of any evidence demonstrating that KADIAN® treatment results in a positive impact in these areas.

******

Please see the enclosed full Product Information for KADIAN®. If you have any questions about KADIAN® or this letter, please consult with your doctor or call 1-877-637-4629.

Sincerely,

Doug Boothe
Chief Executive Officer
Actavis Inc

ATTACHMENT 3

actavis
creating value in pharmaceuticals

IMPORTANT:
Correction of Drug Information about
KADIAN® (morphine sulfate extended-release) Capsules, CII

June __, 2010

Dear Healthcare Professional,

Between June 2009 and February 2010, Actavis sales representatives distributed KADIAN® promotional material that contained representations that were the subject of a Warning Letter from the U.S. Food and Drug Administration ("FDA") on February 18, 2010. The cover page of this material read: "Why settle for generic MS Contin® tablets..." Additionally, from May 2009 until May 2010, Actavis telemarketing representatives contacted physicians and promoted KADIAN® using similar representations.

In the Warning Letter, FDA raised the following concerns regarding the material: (1) it omitted and minimized serious risks associated with KADIAN®; (2) it broadened KADIAN®'s indication and failed to present limitations to its approved indication; and (3) it presented unsubstantiated superiority claims. Actavis ceased using and distributing this material.

Actavis would like to correct and clarify the representations made in its promotional material titled, "Why settle for generic MS Contin® tablets..." and by its telemarketing representatives. Please note that the issues discussed below also apply to other KADIAN® promotional materials distributed between June 2009 and February 2010, including: (1) the KADIAN® Visual Aid; (2) a KADIAN® Conversion Guide; and (3) a material titled "Behind the Scenes, the KADIAN® Capsules Story." Actavis has ceased using or distributing these materials.

I. Broadening of Indication/Failure to State Full Indication

FDA objected to certain representations in the material, stating that these representations suggested that KADIAN® is appropriate to treat broad types of chronic pain.

Please see below the full indication statement for KADIAN®, including limitations on use, as reflected in the Indications and Usage section of the full Prescribing Information:

> 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 (see **CLINICAL PHARMACOLOGY**).
>
> **KADIAN® Capsules are NOT intended for use as a prn analgesic.**

60 Columbia Rd., Bldg. B
Morristown, NJ 07960 (973) 993-4501 www.actavis.com

KADIAN® is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. KADIAN® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

II. Omission and Minimization of Risk Information

FDA stated that while the materials include information from the boxed warning and some adverse reactions associated with KADIAN®, the materials failed to include other important and serious risk information.

Please see below the most important and serious risks associated with KADIAN®, and please refer to the enclosed full Prescribing Information for additional discussion of these risks:

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.

Other important and serious risks associated with KADIAN® include:

Contraindictions:

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.

Warnings:

Care should be taken in the prescribing of this capsule strength. 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.

Misuse, Abuse and Diversion of Opioids
KADIAN® contains morphine an opioid agonist and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Morphine 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.

Abuse of KADIAN® by crushing, chewing, snorting or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND DEPENDENCE** sections in the full Prescribing Information)

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse
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.

Impaired Respiration
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.

Head Injury and Increased Intracranial Pressure
The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. 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.

Hypotensive Effect
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 also **PRECAUTIONS - Drug Interactions**.) 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.

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
KADIAN® is intended for use in patients who require continuous, around-the-clock opioid analgesia for an extended period of time. As with any potent opioid, it is critical to adjust the dosing regimen for KADIAN® for each patient, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of the initial dose of KADIAN®, attention should be given to the points under **DOSAGE AND ADMINISTRATION**.

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.

Selection of patients for treatment with KADIAN® should be governed by the same principles that apply to the use of any potent opioid analgesics. Specifically, the increased risks associated with its use in the following populations should be considered: the elderly or debilitated and those with severe impairment of hepatic, pulmonary, or renal function; hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychosis; prostatic hypertrophy, or urethral stricture; acute alcoholism; delirium tremens; kyphoscoliosis, or inability to swallow.

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.

Cordotomy
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.

Use in Pancreatic/Biliary Tract Disease
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 and Physical Dependence
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.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy** in the full Prescribing Information).

Special Risk Groups
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.

Driving and Operating Machinery
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** in the full Prescribing Information)

III. Unsubstantiated Superiority Claims and Unsubstantiated Effectiveness Claims

FDA objected to representations in the materials that made comparisons between KADIAN® and MS Contin® (morphine sulfate controlled-release) Tablets, CII, Avinza® (morphine sulfate extended-release), Capsules, CII, and generic controlled-release morphine tablets.

FDA objected to these representations as misleading, and objected to any representation in the distributed materials that KADIAN® is safer or more effective than these other products because the references cited in support of these claims do not represent substantial evidence or substantial clinical experience. FDA is not aware of any evidence demonstrating that KADIAN® treatment results in less breakthrough pain, more consistent pain relief, or fewer barriers to prescribing than any other approved extended-release morphine product.

******

Please see the enclosed full Prescribing Information for KADIAN®.

If you have any questions, please call 1-877-637-4629.

Sincerely,

Doug Boothe
Chief Executive Officer
Actavis US

********** -COMM. JOURNAL- ********** DATE JUN-09-2010 ***** TIME 22:22 *********

MODE = MEMORY TRANSMISSION START=JUN-09 22:16 END=JUN-09 22:22

FILE NO.=807

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	913018478444	026/026	00:05:26

-ACTAVIS -

********** -REGULATORY AFF - ***** - 908 659 2250- *********

Fax message

To	Elaine Hu Cunningham, Pharm.D., Senior Regulatory Review Officer CDER, DDMAC Communications		
Date	06/10/10	Fax No	301-847-8444
No of pages (including this one)	26		
Subject	NDA 20-616 / MACMIS #18148		
From	Terri Nataline, Vice President, Regulatory and Medical Affairs		

Hard copy to follow via UPS Overnight Courier.

actavis
creating value in pharmaceuticals

Fax message

To	Elaine Hu Cunningham, Pharm.D., Senior Regulatory Review Officer CDER, DDMAC Communications		
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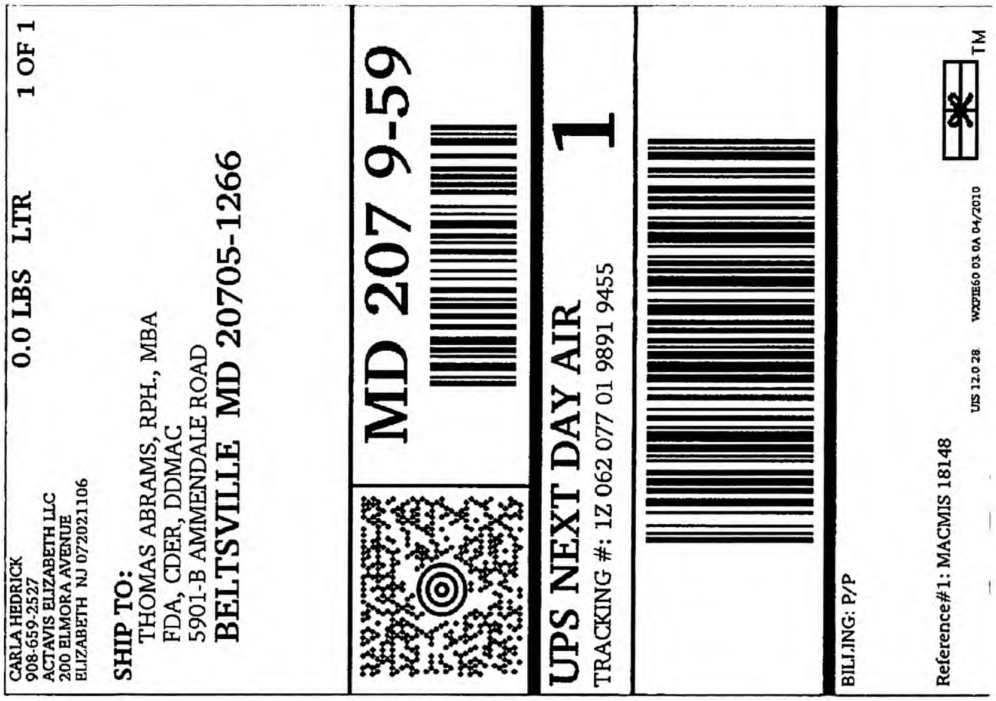
Hard copy to follow via UPS Overnight Courier.



Proof of Delivery

Dear Customer,

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

Tracking Number:	1Z0620770198919455
Reference Number(s):	MACMIS 18148
Service:	NEXT DAY AIR
Shipped/Billed On:	06/10/2010
Delivered On:	06/11/2010 8:53 A.M.
Delivered To:	5901B AMMENDALE RD BELTSVILLE, MD, US 20705
Signed By:	WADE

Location: RECEIVER

Thank you for giving us this opportunity to serve you.

Sincerely,

UPS

Tracking results provided by UPS: 06/14/2010 10:29 A.M. ET

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Terri Nataline
Vice President, Regulatory and Medical Affairs
Actavis US
60 Columbia Road, Building B
Morristown, NJ 07960

RE: *NDA 020616*
Kadian® (morphine extended-release) Capsules, CII
MACMIS #18148

Dear Ms. Nataline:

This letter responds to Actavis Elizabeth LLC's (Actavis) June 10, 2010, letter submitted to the Division of Drug Marketing, Advertising, and Communications (DDMAC) in response to DDMAC's May 20, 2010, letter requesting revisions to Actavis' May 3, 2010, proposed dissemination plan. Reference is made to the February 18, 2010, DDMAC Warning Letter for Kadian® (morphine extended-release) Capsules, CII (Kadian).

We appreciate the additional information you have provided in your June 10, 2010 letter. We have reviewed your responses and proposed revisions and offer the following comments:

Dissemination Plan for Dear Consumer Letter

- We acknowledge your proposal to expand the scope of your dissemination of the Dear Consumer letter to include *all* healthcare professionals' offices that received the Co-Pay Assistance Program Brochure (approximately 10,000 offices and 558 pharmacies), regardless of whether patients from that office redeemed the co-pay cards or not. We appreciate your proposal and have no further comments at this time.

- We acknowledge your proposal to have Actavis representatives physically visit each of the approximately 10,000 healthcare professionals' offices and 558 pharmacies that received the Co-Pay Assistance Program Brochure to set up a stand in the waiting room or waiting area with 25 copies of the Dear Consumer letter. In addition, you propose to have an Actavis representative follow-up with a monthly telephone call or physical visit to each healthcare professional's office during the 90-day corrective period to ensure that sufficient copies of the Dear Consumer letters are available after the initial visit. Should more copies be needed, you propose to mail replacement copies to the office. Moreover, you propose to provide a telephone number for the healthcare professionals' offices to call in the event they need additional copies of the letter. We request that you confirm that your representatives will also follow-up with each of the *pharmacies* with a monthly telephone call or physical visit to ensure that sufficient copies of the Dear Consumer letters are available after the initial visit.

- You propose to begin visits to each healthcare professional's office or pharmacy over an eight-week time period following the final agreement with DDMAC regarding the dissemination plan and completion of a training program with your existing and temporary sales force. We appreciate your proposal and have no further comments at this time.

Dissemination Plan for the Dear Healthcare Professional (DHP) Letter

- We acknowledge the information you provided regarding promotional activities conducted by your telemarketing team that were discovered subsequent to our May 20, 2010 letter that included content in the telemarketing script that were same or similar to the violations cited in the Warning Letter. In addition, we acknowledge that you have ordered the telemarketing team to cease all activities and that the script is being submitted on FDA Form-2253. We have reviewed the actions you have taken thus far to address the promotional activities conducted by your telemarketing team and have no further comments at this time.

- We acknowledge your proposal to expand the scope of your dissemination of the DHP letter (from the 1,900 healthcare professionals who received the Comparison Detailer) to include healthcare professionals' offices that were the subject of a completed call from a telemarketing representative. We further acknowledge that the total number of healthcare professionals exposed to either the completed call or the Comparison Detailer is between 6,200 and 8,100 and that Actavis is currently working to determine the final numbers by removing any duplications. We appreciate your proposal and request that you confirm the final number of healthcare professionals exposed to either the completed call or the Comparison Detailer.

Dear Consumer Letter

We considered your proposed, revised Dear Consumer letter. However, we recommend that the Dear Consumer letter that you submitted on May 3, 2010 (that DDMAC subsequently found acceptable in our letter dated May 20, 2010) be used for dissemination.

In addition, we acknowledge your proposal to re-locate the patient instructions to not discontinue Kadian without first talking to their healthcare professionals from the "Risks" section of the Dear Consumer letter to the introduction section. We would not object to the following underlined revisions to be made on page one of the Dear Consumer letter:

> Actavis would like to take the opportunity to correct and clarify the statements and representations about Kadian made in the Brochure.
>
> Do not stop taking Kadian or any other opioid without talking to your healthcare professional. Kadian can cause physical dependence. This means you could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addiction. Your doctor can tell you more about the differences between physical dependence and drug addiction.

Dear Healthcare Professional (DHP) Letter

We considered your proposed, revised DHP letter. However, we recommend that the DHP letter that you submitted on April 9, 2010 (that DDMAC subsequently found acceptable in our letter dated April 19, 2010) be used for dissemination.

In addition, we acknowledge your proposal to address healthcare professionals who answered a call from Actavis telemarketing representatives in addition to the healthcare professionals who received the Comparison Detailer and similar promotional materials. We would not object to the following underlined revisions to be made on page one of the DHP letter:

> Between June 2009 and February 2010, Actavis sales representatives distributed KADIAN® promotional materials that contained claims and presentations that were the subject of a Warning Letter (dated February 18, 2010) issued by the U.S. Food and Drug Administration ("FDA"). The cover page of this material read: "Why settle for generic MS Contin® tablets. . . ." Additionally, from May 2009 until May 2010, Actavis telemarketing representatives contacted physicians and promoted KADIAN using similar claims and presentations.
>
> . . .
>
> Actavis would like to take the opportunity to correct and clarify the statements and representations made in its promotional material titled, "Why settle for generic MS Contin® tablets. . ." and by its telemarketing representatives. Please note that the issues discussed below apply to other Kadian promotional materials distributed between June 2009 and February 2010, including. . . .

Please submit a written response to this letter on or before July 20, 2010. The response should include a revised dissemination plan and finalized Dear Consumer and DHP letters.

Please direct your response to me at the 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, facsimile at (301) 847-8444.
In all future correspondence regarding this matter, please refer to MACMIS #18148 in addition to the NDA number.

We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

Sincerely,

{See appended electronic signature page}

Elaine Hu Cunningham, Pharm.D.
LCDR, United States Public Health Service
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20616	ORIG-1	ACTAVIS ELIZABETH LLC	KADIAN (MORPHINE SULFATE) ER CAPS 20/50

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELAINE H CUNNINGHAM
07/06/2010

FILE COPY

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Confidential -- Not For Public Disclosure

July 16, 2010

VIA OVERNIGHT MAIL DELIVERY
CONFIRMATION VIA FACSIMILE

Elaine Hu Cunningham, Pharm.D.
LCDR, United States Public Health Service
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 20-616
Kadian® (morphine sulfate extended-release) Capsules, CII
MACMIS #18148

Dear Ms Cunningham,

Reference is made to the Division of Drug Marketing, Advertising, and Communication's (DDMAC) July 6, 2010 letter in response to Actavis Elizabeth LLC's (Actavis) June 10, 2010 submission providing a revised dissemination plan and revised Dear Healthcare Professional (DHP) and Dear Consumer letters. Further reference is made to the February 18, 2010 DDMAC Warning Letter for Kadian® (morphine extended-release) Capsules, CII (Kadian).

In its July 6th letter, DDMAC requested clarification from Actavis regarding two aspects of its revised dissemination plan. It also recommended that Actavis revert to previously submitted versions of its DHP and Dear Consumer letters. Actavis is providing the following in response.

Revised Dissemination Plan for the Dear Consumer Letter

In its revised dissemination plan submitted on June 10, 2010, Actavis proposed physical visits by an Actavis representative to each of the approximately 10,000 healthcare professionals' offices and 558 pharmacies that received a Co-Pay Assistance Program Brochure to set up a stand in the waiting room or waiting area with 25 copies of the Dear Consumer letter. It also proposed to follow-up with monthly visits or telephone calls to the healthcare professionals' office to ensure sufficient copies of the Dear Consumer letter are available after the initial visit. In its July 6th letter, DDMAC asked Actavis to confirm whether a representative will follow up with each pharmacy.

Actavis Elizabeth LLC
A Watson Inc. | 200 Elmora Avenue
Elizabeth, NJ 07207 | 908 527 9100
908 659 2250 | www.actavis.com

Actavis confirms that its revised dissemination plan requires a representative to follow-up with monthly visits or telephone calls to each of the 558 pharmacies to ensure that there is an adequate supply of Dear Consumer letters available at these locations after the initial visit.

Revised Dissemination Plan for the Dear Healthcare Professional Letter

Actavis' revised dissemination plan for the DHP letter encompasses healthcare professionals that received the Comparison Detailer and healthcare professionals' offices that were the subject of a completed call from an Actavis telemarketing representative. In its June 10th submission, Actavis stated that the total number of healthcare professionals that received either the Comparison Detailer or were the subject of completed call was between 6,200 and 8,100. It committed to providing DDMAC with a final number once duplicates were removed.

Please be advised that the final number of healthcare professionals that received either the Comparison Detailer or were the subject of a completed call is 7,163.

Dear Consumer Letter

Provided in Attachment 1 is the final version of Actavis' Dear Consumer Letter. This letter is essentially the same as the letter Actavis submitted on May 3, 2010 except for the paragraph, "Do not stop taking KADIAN®..." is re-located to the first page as DDMAC suggested. Actavis also corrected the toll-free telephone number that consumers can use to ask questions. Please note that the full prescribing information will be attached to each Dear Consumer Letter.

Dear Healthcare Professional Letter

Actavis has revised the DHP letter it previously submitted on April 9, 2010 to incorporate the changes recommended by DDMAC. These changes address the healthcare professionals who answered a call from Actavis telemarketing representatives in addition to healthcare professionals who received the Comparison Detailer. Please note that the toll-free telephone number was also corrected. The final DHP letter is provided in Attachment 2. The full prescribing information will accompany each DHP letter in the same manner as shown in Attachment 3 to Actavis' May 3, 2010 response.

Actavis appreciates DDMAC's comments and suggestions for improving Actavis' corrective messages. Actavis trusts that DDMAC will find the revised dissemination plan and corrective letters address all of the outstanding issues raised in the Warning Letter.

Sincerely,

Terri Nataline
Vice President, Regulatory and Medical Affairs
Actavis US

NDA 20-616
Kadian® (morphine sulfate extended-release) Capsules, CII
MACMIS #18148

Enclosures

Doug Boothe
Chief Executive Officer
Actavis US

John LaRocca
Chief Legal Officer
Actavis US

ATTACHMENT A

actavis

creating value in pharmaceuticals

IMPORTANT:
Correction of Drug Information about
KADIAN® (morphine sulfate extended-release) Capsules, CII

July__, 2010

Dear Valued Consumer,

You are receiving this letter because you may have received from Actavis a Co-Pay Assistance Program Card which was attached to a Co-Pay Assistance Program Brochure. This letter specifically concerns the Co-Pay Assistance Program Brochure ("Brochure"), which was the subject of a Warning Letter issued by the U.S. Food and Drug Administration ("FDA") on February 18, 2010.

In the Warning Letter, FDA raised the following concerns about the Brochure: (1) it left out and minimized serious risks associated with KADIAN®; (2) it claimed KADIAN® was approved by FDA for conditions it is not approved for; and (3) it presented unsupported claims about how well it works.

Actavis would like to take the opportunity to correct and clarify the statements and representations about KADIAN® made in the Brochure.

Do not stop taking KADIAN® or any other opioid without talking to your healthcare professional. KADIAN® can cause physical dependence. This means you could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addiction. Your doctor can tell you more about the differences between physical dependence and drug addiction.

I. Indication

FDA objected to the general discussion in the Brochure regarding "chronic pain" and "pain management," stating that this discussion suggested that KADIAN® is appropriate to treat all types of chronic pain.

Please note that KADIAN® is indicated to treat only certain types of pain. Specifically:

> KADIAN® capsules are an extended-release capsule taken by mouth of morphine sulfate that is used to manage moderate to severe pain that continues around-the-clock and is expected to last for an extended period of time.
>
> **KADIAN® is NOT for use to treat pain that occurs once in a while ("as needed").**

actavis, inc. | 60 Columbia Rd., Bldg. B Morristown, NJ 07960 | (973) 993-4501 | www.actavis.com

KADIAN® is not indicated for pain in the immediate post-operative period (12-24 hours following surgery) for patients who have not taken drugs called opioids before.

KADIAN® is not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

Please remember to consider the above information about the appropriate use of KADIAN®, including its limitations on use, and discuss these issues with your doctor.

II. Risks

FDA stated that while the Brochure mentioned certain risks associated with KADIAN® (including information on its boxed warning (see below)), the Brochure failed to include other important and serious risk information. Moreover, FDA objected to the Brochure's use of medical language to explain these risks to patients because such information may not be easily understood.

Please see below a discussion of the most important and serious risks associated with KADIAN®, and please refer to the enclosed full Prescribing Information for additional discussion of these risks.

A. In The FDA Approved Prescribing Information for Healthcare Providers:

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.

B. What This Means for You:

Most Important Information to Know About KADIAN®

- KADIAN®, which is a federally controlled substance (CII), can be abused by people who abuse prescription medicines or street drugs. To prevent theft, misuse, or abuse of KADIAN®, keep it in a safe place. Do not give KADIAN® to anyone else. It may harm them or even cause death. After you stop taking KADIAN®, flush any unused capsules down the toilet.

- Do not crush, dissolve, or chew KADIAN® capsules or the capsule contents before swallowing. Abuse of KADIAN® by crushing, chewing, snorting or injecting the dissolved product will result in the uncontrolled delivery of morphine and pose a significant risk to the abuser that could result in overdose or death.

- KADIAN® is **NOT** for use to treat pain that occurs once in a while ("as needed").

- KADIAN® 100 mg and 200 mg capsules are for use only in opioid tolerant patients. "Opioid tolerant" means that you regularly use another opioid medicine for constant pain and that your body is used to it. **Ingesting KADIAN® 100 mg and 200 mg capsules when you are not opioid tolerant may cause serious breathing problems and death.**

Do Not Take KADIAN® If:

- You have a known hypersensitivity (allergy) to morphine, morphine salts, or any of the ingredients in KADIAN® (See the accompanying Prescribing Information for a complete list of ingredients in KADIAN®).

- You are having an asthma attack or have severe asthma, trouble breathing, or lung problems.

- You have a bowel blockage called paralytic ileus.

- Do not take KADIAN® with alcohol, other opioids, or illicit drugs because dangerous additive effects may occur resulting in serious injury or death. In addition, alcohol can cause very high levels of morphine in your blood and you can die due to an overdose of morphine.

Possible Side Effects of KADIAN®

- KADIAN® can cause serious breathing problems that may be life-threatening, especially if KADIAN® is used in the wrong way. Call your healthcare professional or get medical help right away if your breathing slows down, you have shallow breathing, you feel faint, dizzy, confused, or have any unusual symptoms. These can be symptoms that you have taken too much KADIAN® or that the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

- There is a chance of abuse or addiction with KADIAN®.

- Serious allergic reactions, while extremely rare, have been reported with use of KADIAN®. Get medical help right away if you experience any symptoms of a severe allergic reactions, such as: feeling dizzy or faint, trouble breathing, chest pain, or swelling of the face, throat, or tongue.

- Do not drive or operate machinery or perform other potentially hazardous activities until you know how you react to this medicine or a change in the dose.

Please Remember

- These are not all the risks and side effects associated with KADIAN®. For more information, please contact your doctor.

- Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

III. Unsubstantiated Effectiveness Claims

FDA objected to the following statements in the Brochure regarding chronic pain:

- ". . . Many Americans suffer from chronic or ongoing pain. It can cause you to miss work and can even keep you from enjoying life. If left untreated, pain can place stress on your body and your mental health . . . ."

- " . . . Chronic pain . . . can be inconvenient and can keep you from your daily tasks."

FDA stated that the above representations suggested that use of KADIAN® results in a positive impact on a patient's work, physical and mental functioning, daily activities, or enjoyment of life. FDA stated that these representations were misleading because they suggested that KADIAN® is more effective than has been demonstrated. FDA is not aware of any evidence demonstrating that KADIAN® treatment results in a positive impact in these areas.

******

Please see the enclosed full Prescribing Information for KADIAN®. If you have any questions regarding KADIAN® or this letter, please consult with your doctor or call 1-888-496-3082.

Sincerely,

Doug Boothe
Chief Executive Officer
Actavis Inc.

KADIAN® is a registered trademark of Actavis Elizabeth LLC

ATTACHMENT B

actavis

creating value in pharmaceuticals

IMPORTANT:
Correction of Drug Information about
KADIAN® (morphine sulfate extended-release) Capsules, CII

July __, 2010

Dear Healthcare Professional,

Between June 2009 and February 2010, Actavis sales representatives distributed KADIAN® promotional materials that contained claims and presentations that were the subject of a Warning Letter (dated February 18, 2010) issued by the U.S. Food and Drug Administration ("FDA"). The cover page of this material read: "Why settle for generic MS Contin® tablets...." Additionally, from May 2009 until May 2010, Actavis telemarketing representatives contacted physicians and promoted KADIAN® using similar claims and presentations.

In the Warning Letter, FDA raised the following concerns regarding the material: (1) it omitted and minimized serious risks associated with KADIAN®; (2) it broadened KADIAN®'s indication and failed to present limitations to its approved indication; and (3) it presented unsubstantiated superiority claims. Upon receiving this letter, Actavis immediately ceased using or distributing this material.

Actavis would like to take the opportunity to correct and clarify the statements and representations made in its promotional material titled, "Why settle for generic MS Contin® tablets..." and by its telemarketing representatives. Please note that the issues discussed below apply to other KADIAN® promotional materials distributed between June 2009 and February 2010, including: (1) the KADIAN® Visual Aid; (2) a KADIAN® Conversion Guide; and (3) a material titled "Behind the Scenes, the KADIAN® Capsules Story." Actavis has also ceased using or distributing these materials.

I. Broadening of Indication/Failure to State Full Indication

FDA objected to certain representations in the material, stating that these representations suggested that KADIAN® is appropriate to treat broad types of chronic pain.

Please see below the full indication statement for KADIAN®, including limitations on use, as reflected in the Indications and Usage section of the full Prescribing Information:

> 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 (see **CLINICAL PHARMACOLOGY**).

Actavis, Inc. | 60 Columbia Rd., Bldg. B Morristown, NJ 07960 | (973) 993-4501 | www.actavis.com

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

KADIAN® is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. KADIAN® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

II. Omission and Minimization of Risk Information

FDA stated that while the material disclosed certain risks (including information on the boxed warning), the material failed to include other important and serious risk information.

Please see below the most important and serious risks associated with KADIAN®, and please refer to the enclosed full Prescribing Information for additional discussion of these risks:

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.

Other important and serious risks associated with KADIAN® include:

Contraindictions:

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.

Warnings:

KADIAN® Capsules are to be swallowed whole and are not to be chewed, crushed, or dissolved. Taking chewed, crushed, or dissolved KADIAN®® Capsules leads to rapid release and absorption of a potentially fatal dose of morphine.

KADIAN® 100 mg and 200 mg Capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. This capsule strength may cause fatal respiratory depression when ingested or administered to patients who are not previously exposed to opioids.

Care should be taken in the prescribing of this capsule strength. 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.

Misuse, Abuse and Diversion of Opioids
KADIAN® contains morphine an opioid agonist and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Morphine 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.

Abuse of KADIAN® by crushing, chewing, snorting or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND DEPENDENCE** sections in the full Prescribing Information)

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse
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.

Impaired Respiration
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.

Head Injury and Increased Intracranial Pressure
The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. 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.

Hypotensive Effect
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 also **PRECAUTIONS - Drug Interactions**.) 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.

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
KADIAN® is intended for use in patients who require continuous, around-the-clock opioid analgesia for an extended period of time. As with any potent opioid, it is critical to adjust the dosing regimen for KADIAN® for each patient, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of the initial dose of KADIAN®, attention should be given to the points under **DOSAGE AND ADMINISTRATION**.

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.

Selection of patients for treatment with KADIAN® should be governed by the same principles that apply to the use of any potent opioid analgesics. Specifically, the increased risks associated with its use in the following populations should be considered: the elderly or debilitated and those with severe impairment of hepatic, pulmonary, or renal function; hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychosis; prostatic hypertrophy, or urethral stricture; acute alcoholism; delirium tremens; kyphoscoliosis, or inability to swallow.

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.

Cordotomy
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.

Use in Pancreatic/Biliary Tract Disease
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 and Physical Dependence
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.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy** in the full Prescribing Information).

Special Risk Groups
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.

Driving and Operating Machinery
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** in the full Prescribing Information)

III. Unsubstantiated Superiority Claims and Unsubstantiated Effectiveness Claims

FDA objected to several claims in the material that reference MS Contin® (morphine sulfate controlled-release) Tablets, CII, Avinza® (morphine sulfate extended-release), Capsules, CII, and generic controlled-release morphine tablets. Specifically, the material:

- Stated "Why settle for generic MS Contin® tablets…When you can prescribe the benefits of KADIAN® capsules."
- Made claims regarding the superior pharmacokinetic properties of KADIAN® versus generic controlled-release morphine tablets which implied that KADIAN® will lead to less breakthrough pain and more consistent pain relief.
- Made claims regarding "better pain control and improved sleep scores" versus generic controlled-release morphine tablets.
- Made claims about the superior dosing flexibility of KADIAN® versus MS Contin and Avinza which implied that KADIAN® offers fewer barriers to prescribing compared to MS Contin or Avinza.

FDA objected to each of the above claims as misleading, and objected to any representation in the distributed material that KADIAN® is safer or more effective than these other products because the references cited in support of these claims do not represent substantial evidence or substantial clinical experience. FDA is not aware of any evidence demonstrating that KADIAN® treatment results in less breakthrough pain, more consistent pain relief, or fewer barriers to prescribing than any other approved extended-release morphine product.

******

Please see the enclosed full Prescribing Information for KADIAN®. If you have any questions, please call 1-888-496-3082.

Sincerely,

Doug Boothe
Chief Executive Officer
Actavis Inc.

KADIAN® is a registered trademark of Actavis Elizabeth LLC

********** -COMM. JOURNAL- ********** DATE JUL-16-2010 ***** TIME 02:22 *********

MODE = MEMORY TRANSMISSION START=JUL-16 02:19 END=JUL-16 02:22

FILE NO.=890

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
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-ACTAVIS -

********** -REGULATORY AFF - ***** - 908 659 2250- *********

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Fax message

To	Elaine Hu Cunningham, Pharm.D., Senior Regulatory Review Officer CDER, DDMAC Communications		
Date	07/16/10	Fax No	301-847-8444
No of pages (including this one)	16		
Subject	NDA 20-616 / MACMIS #18148		
From	Terri Nataline, Vice President, Regulatory and Medical Affairs		

Hard copy to follow via UPS Overnight Courier.

actavis
creating value in pharmaceuticals

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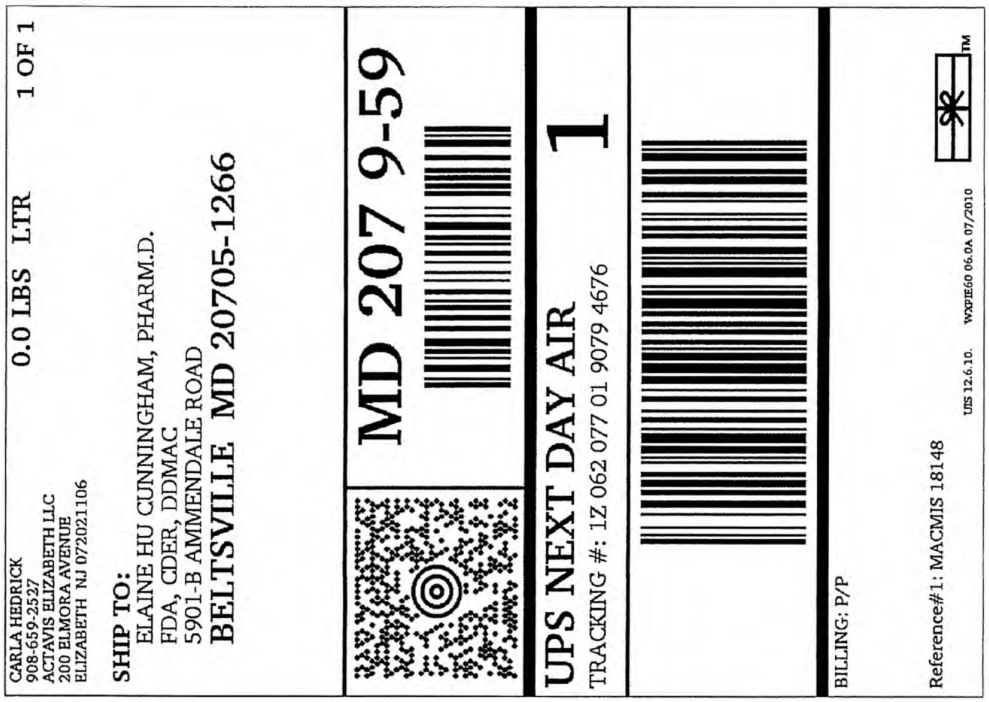

Proof of Delivery

Dear Customer,

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

Tracking Number:	1Z0620770190794676
Reference Number(s):	MACMIS 18148
Service:	NEXT DAY AIR
Shipped/Billed On:	07/16/2010
Delivered On:	07/19/2010 8:47 A.M.
Delivered To:	5901 AMMENDALE RD BELTSVILLE, MD, US 20705
Signed By:	WADE
Location:	RECEIVER

Thank you for giving us this opportunity to serve you.

Sincerely,

UPS

Tracking results provided by UPS: 07/19/2010 10:47 A.M. ET

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF DRUG MARKETING, ADVERTISING, AND COMMUNICATIONS
10903 NEW HAMPSHIRE AVE, BLDG #51
SILVER SPRING, MD 20993

FAX

Date: February 18, 2010

To: **Doug Boothe**
Chief Executive Officer
Actavis US

Fax: **(973) 993-4303**

Phone: **(908) 527-9100**

From: Elaine Hu Cunningham, Pharm.D.,
LCDR, United States Public Health Service
Senior Regulatory Review Officer
Phone: (301) 796-1200
Fax: (301) 847-8444

Subject: **NDA 20-616 / MACMIS #18148**

Pages: **12** (not including cover sheet)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Doug Boothe, Chief Executive Officer
Actavis US
60 Columbia Road, Building B
Morristown, NJ 07960

RE: NDA #20-616
Kadian® (morphine extended-release) Capsules, CII
MACMIS #18148

WARNING LETTER

Dear Mr. Boothe:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a Co-Pay Assistance Program brochure (KAD200901) for Kadian® (morphine extended-release) Capsules, CII (Kadian), submitted by Actavis Elizabeth LLC (Actavis) under cover of Form FDA-2253. DDMAC has also reviewed a PK to PK Comparison Detailer (Comparison Detailer) (KADI8D0231) for Kadian that was originally submitted by Alpharma under cover of Form FDA-2253.[1] The Co-Pay Assistance Program brochure and Comparison Detailer are false or misleading because they omit and minimize the serious risks associated with the drug, broaden and fail to present the limitations to the approved indication of the drug, and present unsubstantiated superiority and effectiveness claims. Therefore, the Co-Pay Assistance Program brochure and Comparison Detailer misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (ii) & (xviii); (e)(7)(i) & (viii). These violations are a concern from a public health perspective because they suggest that the product is safer and more effective than has been demonstrated.

Background

The INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) for Kadian states (emphasis in original):

> 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.**

[1] As of January 8, 2009, NDA 20-616 has been transferred to Actavis US.

KADIAN® is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. KADIAN® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. . . .

Kadian is associated with a number of serious risks, many of which are potentially fatal. The PI includes the following boxed warning concerning potentially fatal overdosing if Kadian capsules are chewed, crushed, or dissolved, and other serious risks (emphasis in original):

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.

The PI states that Kadian is contraindicated in any situation where opioids are contraindicated. This includes patients with respiratory depression in the absence of resuscitative equipment or in unmonitored settings, in patients with acute or severe bronchial asthma or hypercarbia, and in patients who have or are suspected of having paralytic ileus.

The PI includes warnings, in addition to the boxed and bolded warnings, related to the potentially fatal abuse potential of opioids, use by individuals other than the patient for

whom the drug was prescribed, interactions with alcohol and drugs of abuse, impaired respiration, head injury and increased intracranial pressure, hypotensive effect, interactions with other central nervous system (CNS) depressants, gastrointestinal obstruction, and anaphylaxis.

There are a number of precautions associated with Kadian, including the general precautions that it is intended for use in patients who require continuous, around-the-clock opioid analgesia and that it is critical to adjust the dosing regimen taking into account the patient's prior analgesic treatment experience; that 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; that the administration of Kadian may obscure the diagnosis or clinical course in patients with acute abdominal conditions; and that Kadian may aggravate pre-existing convulsions in patients with convulsive disorders. The Kadian PI also include several specific precautions related to cordotomy, use in pancreatic/biliary tract disease, tolerance and physical dependence, use in special risk groups (e.g., elderly or debilitated patients, patients with severe renal or hepatic insufficiency), and risks associated with driving or operating machinery.

The PI outlines several serious drug interactions with Kadian, including CNS depressants, muscle relaxants, mixed agonist/antagonist opioid analgesics, monoamine oxidase inhibitors, cimetidine, and diuretics.

In addition, the ADVERSE REACTIONS section of the PI states that the most serious adverse events occurring in patients taking Kadian include respiratory depression, respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock. The most frequent less severe adverse events include drowsiness, dizziness, constipation, and nausea.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. While the Comparison Detailer and the Co-Pay Assistance Program brochure include information from the boxed warning and some adverse reactions associated with Kadian, they fail to include other important and serious risk information. Specifically, the Comparison Detailer and Co-Pay Assistance Program brochure present several effectiveness claims for Kadian but fail to present any contraindications, and also omit several warnings, precautions, drug interactions and adverse events. For example the promotional materials fail to reveal warnings regarding potentially fatal abuse of opioids, use by individuals other than the patient for whom the drug was prescribed, interactions with alcohol and drugs of abuse, impaired respiration, head injury and increased intracranial pressure, hypotensive effect, interactions with other central nervous system depressants, gastrointestinal obstruction, and anaphylaxis. Similarly, the promotional materials fail to reveal precautions related to use in patients with prior analgesic treatment experience; use in certain patient populations with narrow therapeutic index for opioid analgesics; use in patients with acute abdominal conditions; use in patients with convulsive disorders; use in patients

undergoing cordotomy; use in pancreatic/biliary tract disease; tolerance and physical dependence with use of opioids; use in special risk groups; and risks associated with driving and operating machinery.

The Comparison Detailer also fails to present risk information with a prominence and readability that is reasonably comparable to the presentation of benefit information. Specifically, the first five of the six pages of the Comparison Detailer prominently present efficacy claims about Kadian using large, bolded headers and claims surrounded by a significant amount of white space, and using colorful charts and graphs. However, the only specific risk information presented is relegated to the back cover of the piece. Furthermore, this information is presented in small font in single-spaced paragraph format, and beneath a large, bolded headline claim that presents a benefit claim, "**Prescribe KADIAN® – Less pain for your patients. More options for you**" (emphasis in original). In addition, there are no presentation elements to emphasize to the reader that it is important safety information.

In addition, the Co-Pay Assistance Program brochure minimizes the serious and significant risks associated with the use of Kadian. Specifically, the back cover includes the boxed warning and some information from the ADVERSE REACTIONS section of the PI. However, these serious, potentially fatal risks are presented in highly complex, medically technical language that is not likely to be understood by consumers.

We note that the statement, "***Please see accompanying complete Prescribing Information***" (emphasis in original) appears on various pages of the Comparison Detailer and Co-Pay Assistance Program brochure; however this statement does not mitigate the misleading omission and/or minimization of risk information in the pieces.

The overall effect of these presentations minimizes the risks associated with Kadian and misleadingly suggests that Kadian is safer than has been demonstrated.

Broadening of Indication/Failure to State Full Indication

Promotional materials are misleading if they imply that a drug product is indicated for use in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. The Comparison Detailer and Co-Pay Assistance Program brochure fail to include the complete approved indication for Kadian, and present broad claims about the drug's use in treating pain, therefore implying that Kadian is appropriate for use in a broader range of patients than it is approved to treat. For example, the Comparison Detailer includes the following claims (emphasis in original):

- "**Allow for less breakthrough pain and more consistent pain relief for patients**" (footnote omitted)
- "**Better pain control. . .**"
- "**Improved pain control. . .**"
- "**Allow patients to live with less pain. . .**" (footnote omitted)
- "**Allow individualization and customization of a patient's pain treatment**"
- "**Prescribe KADIAN® – Less pain for your patients. More options for you.**"
- "**Less Pain. More Options.**"

These presentations in the Comparison Detailer suggest that Kadian is appropriate for patients with broader types of pain than the drug is indicated for. Similarly, the Co-Pay Assistance Program brochure includes the following statements (emphasis in original):

- "**Why is pain management important?** Pain management is a large part of your overall health care plan. Many Americans suffer from chronic or ongoing pain . . .Managing your pain the right way begins by talking to your healthcare provider. Discover the cause of your pain by taking note of what makes your pain start and what makes it worse."

- "**What is chronic pain?** Chronic pain is ongoing and can last longer than 6 months. Chronic pain can be mild or severe. . . ."

- "**How can I treat my chronic pain?** To help manage your pain, your healthcare provider will determine what level of pain control you need. Depending on what kind of pain you have and how it affects your life, your healthcare provider will choose a drug that works just for you."

The totality of these presentations in the Co-Pay Assistance Program brochure suggests that patients with broader types of chronic pain than the drug is indicated for are appropriate candidates for Kadian therapy, when this is not the case. These presentations in the two pieces are particularly concerning considering the serious and potentially fatal risks associated with the drug. Kadian is only appropriate for a very limited patient population who experience pain. We note that the partial indication of Kadian is included on the back covers of both pieces (included as warnings in the Comparison Detailer). However, these presentations omit the important limitation that:

> KADIAN® is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. KADIAN® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate.

In addition, the partial indication included on the back cover of the Co-Pay Assistance Program brochure, unlike the chronic pain information, is written in technical medical language that is not likely to be easily understood by consumers. We also note that the statement, "***Please see accompanying complete Prescribing Information***" (emphasis in original) appears on various pages of the Comparison Detailer and Co-Pay Assistance Program brochure; however this statement does not mitigate the implication of the above claims and presentations that broadly promote the use of this drug for any type of pain relief. Therefore, the pieces misleadingly suggest that Kadian can be used for pain relief in a much broader range of patients than has been demonstrated by substantial evidence or substantial clinical experience.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they represent or suggest that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. The Comparison Detailer includes the following efficacy claims and presentations that compare Kadian to MS Contin® (morphine sulfate controlled-release) Tablets, CII (MS Contin) and generic controlled-release morphine (emphasis in original):

- "**Why settle for generic MS Contin® tablets. . .When you can prescribe the benefits of KADIAN® capsules?**"
- "**Fewer peaks and valleys**
  Smooth steady-state plasma levels compared with controlled-release (CR) morphine tablets q12h and q24h"[2] presented in conjunction with the following two graphs:
  - Graph titled, "Pharmacokinetics of **ONCE-DAILY KADIAN®** vs twice-daily CR morphine tablets over 24 hours"[2,3] that displays normalized mean steady-state plasma morphine concentration (ng/mL) over time (hours) of Kadian and CR morphine tablets.
  - Graph titled, "Pharmacokinetics of **TWICE-DAILY KADIAN®** vs twice-daily CR morphine tablets over 12 hours"[2,3] that displays normalized mean steady-state plasma morphine concentration (ng/mL) over time (hours) of Kadian and CR morphine tablets.
- "**Allow for less breakthrough pain and more consistent pain relief for patients**"[3]

The above claims and presentations misleadingly imply that Kadian has been shown to be superior to MS Contin or generic controlled-release morphine because Kadian's pharmacokinetic properties will lead to less breakthrough pain and more consistent pain relief. FDA is not aware of any substantial evidence or substantial clinical experience that supports these claims and presentations. If you have data to support these claims, please submit the data to FDA for review.

The Comparison Detailer references Kadian's PI to support the above claims and presentations. The CLINICAL PHARMACOLOGY, Pharmacokinetics and Absorption sections of the PI include data from 48 patients with pain related to malignancy that were enrolled in two pharmacokinetic studies. The results from these two studies suggest less fluctuation in steady-state plasma concentrations (C_{max}-C_{min}/C_{min}) normalized to 100 mg every 24 hours in patients who were given Kadian compared with patients who were given twice daily controlled-release morphine tablets. However, the clinical consequences of these

[2] KADIAN® [current prescribing information].
[3] Gourlay GK, Cherry DA, Onley MM, et al. Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly MS Contin in the treatment of severe cancer pain. *Pain*. 1997;69(3):295-302.

pharmacokinetic differences were not studied and are not known. It is at least possible that the earlier and higher peak leads of MS Contin could represent an advantage absent clinical pain data. The pharmacokinetic data presented within the PI do not constitute substantial evidence to support any claims of clinical superiority such as those described above.

The Comparison Detailer also references the Gourlay, et al. article, which describes one of the pharmacokinetic studies presented in the PI (Study# MOR-9/92), to support the above claims and presentations. The study results in the Gourlay, et al. article reported that patients who were given Kadian had significantly higher C_{min} concentrations, less fluctuation in plasma morphine concentrations throughout the dosing interval, and a greater time that plasma concentrations were ≥75% of C_{max} compared to patients who were given MS Contin. Unlike the PI, Gourlay, et al. also reports pain results from this study. Gourlay, et al. found no significant differences between Kadian and MS Contin in any of the steady-state (day seven) primary clinical parameters (i.e., percent taking rescue medication, time to first rescue dose, total strength of rescue dose, and percent total 24-hour morphine dose as rescue dose). In addition, there were no differences in steady-state secondary parameters, including verbal rating scale for pain intensity and control or visual analog pain scores. The Gourlay, et al. article thus provides no support for the idea that the pharmacokinetic differences between Kadian and MS Contin had any clinical consequences.

In addition, the Comparison Detailer includes the following pain and sleep-related claims and presentations that compare Kadian to MS Contin and generic controlled-release morphine (emphasis in original):

- "**Better pain control and improved sleep scores**"
- "**Improved pain control and sleep scores in patients treated with KADIAN® who were previously on CR morphine tablets**"[4*] presented in conjunction with the following two graphs:
  - Graph titled, "Significant **PAIN REDUCTION**"[4] that displays a "**36% improvement in pain score**"[4] (scale 0-10: 0=no pain; 10=worst pain imaginable) from baseline in patients switched from MS Contin to Kadian.
  - Graph titled, "Significant **REDUCTION IN SLEEP INTERFERENCE**"[4] that displays a "**47% improvement in sleep score**"[4] (scale 0-10: 0=did not interfere with sleep at all; 10=completely interfered with sleep) from baseline in patients switched from MS Contin to Kadian.
- "**Allow patients to live with less pain and get adequate rest with less medication**"[4]

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[4] Weil A, Nicholson B, Ross E, Sasaki J. Patients with chronic, non-malignant, moderate/severe pain can be successfully switched from other sustained-release morphine or oxycodone compounds of Kadian® (morphine sulfate sustained-release capsules): the KRONUS-MSP trial. Poster presented at: American Pain Society 23rd Annual Scientific Meeting; May 6-9, 2004; Vancouver, BC.

* In a subanalysis of a randomized, open-label, blinded endpoint study of patients previously taking CR morphine tablets and switched to KADIAN® capsules.

These claims are supported by a historically controlled study of inadequate design, completely lacking any concurrent control. The above claims and presentations misleadingly imply that Kadian is superior to MS Contin and generic controlled-release morphine because Kadian provides better pain control and a reduction in sleep interference compared to MS Contin and generic controlled-release morphine. FDA is not aware of any substantial evidence or substantial clinical experience to support such a claim.

The Comparison Detailer references the Weil, et al. poster presentation[4] to support the above claims and presentations. This reference discusses the KRONUS-MSP trial—a study that was not published. Data for the KRONUS-MSP trial was derived from a community-based, prospective, open-label, blinded endpoint trial that included a subset of patients who were previously and unsuccessfully treated with either MS Contin (n=55) or OxyContin® (oxycodone HCl controlled-release) Tablets, CII (OxyContin) (n=150). The patients were randomized to receive either morning or evening daily dosing with Kadian during a four-week treatment period. No patients were randomized to MS Contin or OxyContin. For several reasons, the cited reference fails to support any claim of superiority of Kadian to MS Contin. We note that referring to this trial as "randomized" is itself misleading, as a reader would surely assume that randomization was to two drug treatments, not to morning and evening dosing, a distinction not remotely relevant to the data presented.

The study compared pain reduction and interference of pain with sleep in people reported to have had a poor response to prior treatment with MS Contin or OxyContin. An appropriate study design to investigate this question would have randomized patients to Kadian or MS Contin. A finding in such a properly designed study of greater effect on pain or sleep would not support a general claim of superiority but could support the value of Kadian in MS Contin poor responders. The trial as conducted, however, compared results on open-label treatment with Kadian with an historical control MS Contin cohort. This is a completely meaningless comparison. It is commonly observed that patients given a placebo in trials improve compared to their pre-trial state. That is why, in symptomatic continuous pain, a concurrent control group is essential.

Overall, data from the KRONUS-MSP trial clearly do not support any conclusion that Kadian is superior to alternative treatments in pain or sleep measures. The trial was an exploratory open-label study with no comparators; thus, no conclusions can be inferred. If you have data from adequate and well-controlled trials to support these claims, please submit them to FDA for review.

Finally, the Comparison Detailer includes the following dosing claims and presentations that compare Kadian with both MS Contin and AVINZA® (morphine sulfate extended-release capsules), CII (Avinza) (emphasis in original):

- "**Fewer barriers to prescribing**
  The unique dosing flexibility of KADIAN® gives you more options with a morphine"[2,5,6] presented in conjunction with a chart comparing the available capsule and tablet dose strengths for Kadian, MS Contin, and Avinza.

- Claims below the chart include the following:

  - "No immediate-release (IR) component"
  - "No ceiling dose—contains no acetaminophen, ibuprofen, or fumaric acid"[2]
  - "Allows for titration in increments of 10 mg, with a low dose of 10 mg"[2]
  - "**Allow individualization and customization of a patient's pain treatment**"

These claims are misleading because they imply that Kadian is superior to both MS Contin and Avinza because Kadian's dosage strength availability (i.e., eight dosage strengths in 10, 20, 30, 50, 60, 80, 100, and 200 mg capsules) offers "fewer barriers to prescribing," and because Kadian has no immediate release component, no ceiling dose, and allows for 10 mg titration increments. The Comparison Detailer references the PIs for Kadian, Avinza, and MS Contin to support these claims. However, FDA is unaware of any substantial evidence or substantial clinical experience to support the claim that the above dosing characteristics allow Kadian to have "fewer barriers to prescribing" (the meaning of which is not clear) as compared to other extended-release morphine products. There is no evidence to support that small increments in dosage strength (i.e., 10 mg) would offer a clinical advantage for Kadian in patients who are taking an opioid chronically, particularly as Kadian may need to be dosed more often than some of the comparators (e.g., twice a day versus once a day for Avinza). There is no evidence to support that an immediate-release component would limit the use of a morphine product. Finally, the claim suggesting that Kadian offers fewer barriers to prescribing because it does not contain acetaminophen, ibuprofen, or fumaric acid is misleading because this characteristic of Kadian does not offer any advantages over other extended-release morphine products. Specifically, none of the extended-release morphine products contain acetaminophen or ibuprofen, and while Avinza contains fumaric acid, there is no evidence to suggest that the resulting limiting dose would pose any restrictions on the typical patient population for which the drug is indicated.

Unsubstantiated Effectiveness Claims

Promotional materials are misleading if they contain representations that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The Co-Pay Assistance Program brochure includes the following presentations:

- ". . . Many Americans suffer from chronic or ongoing pain. It can cause you to miss work and can even keep you from enjoying life. If left untreated, pain can place stress on your body and your mental health. . . ."

- ". . . Chronic pain . . . can be inconvenient and can keep you from your daily tasks."

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[5] AVINZA® [prescribing information]. Bristol, TN: King Pharmaceuticals Inc; October 2005.
[6] MS Contin® [prescribing information]. Stamford, CT: Purdue Pharma LP; August 2007.

FDA acknowledges that the treatment of patients in pain is a critical aspect of medical practice. Although Kadian may help treat patients' moderate to severe pain, we are not aware of substantial evidence or substantial clinical experience demonstrating that the magnitude of the effect the drug has in alleviating pain, taken together with any drug-related side effects patients may experience (such as the common adverse events of drowsiness, dizziness, constipation and nausea), results in an overall positive impact on a patient's work, physical and mental functioning, daily activities, or enjoyment of life. In addition, we are not aware of any studies demonstrating that the level of pain reduction experienced by patients on Kadian therapy corresponds with a positive impact on the outcomes claimed. If you have data to support these claims, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the Comparison Detailer and Co-Pay Assistance Program brochure misbrand Kadian in violation of the Act, 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (ii) & (xviii); (e)(7)(i) & (viii).

DDMAC requests that Actavis immediately cease the dissemination of violative promotional materials for Kadian such as those described above. Please submit a written response to this letter on or before March 4, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Kadian that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials.

Please direct your response to me at the 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, facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to MACMIS#18148 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Kadian comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20616	ORIG-1	ACTAVIS ELIZABETH LLC	KADIAN (MORPHINE SULFATE) ER CAPS 20/50

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS W ABRAMS
02/18/2010