From: Terri Nataline
To: Michael Clarke
Sent: 2/2/2012 2:04:31 PM
Subject: Kadian Warning Letter/ QRx CMO
Attachments: Kadian Warning Letter.pdf

Michael,

Below is the info on QRx's Chief Medical Officer. Also attached is the Kadian Warning letter. Definitely a low point.

Patricia Richards, MD, PhD

Chief Medical Officer

Patricia Richards, MD, PhD is a noted expert in pain management and CNS drug development. She has a long-term interest in CNS pharmacology and currently serves as Chief Medical Officer ofQRx Pharma.

Prior to joining QRx, she was Chief Medical Officer of JDS Pharma, a psychiatry specialty company, Vice President of Clinical Development of AlgoRx Pharmaceuticals, a pain drugdevelopment company, and several years at Purdue Pharma where she was instrumental in leading theworldwide development of Oxycontin including drug approvals in Germany, the United Kingdom and approximately 12 other EU countries as well as Japan and Korea. While at Purdue, Dr. Richards designed and successfully completed several Phase 4 studies that for the first time showed an opioid drug could be efficacious in treating neuropathic pain.

Prior to entering the pharmaceutical industry, Dr. Richards was a faculty member and researcher in pain management at New York University. She also had extensive clinical experience as an anesthesiologist and pain specialist in privatepractice for nine years during which she was the chief of the largest pain clinic in Georgia. Dr. Richards completed residencies and board certification in Internal Medicine, Anesthesiology andspecial certification in Pain Management at Johns Hopkins Hospital and then was a faculty memberat Johns Hopkins where her research involved the treatment of pancreatic cancer pain.

Terri Nataline
Vice President, Regulatory and Medical Affairs

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PLAINTIFFS TRIAL EXHIBIT
P-27818_00001


actavis
think smart medicine

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 <u>any</u> 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

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[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