actavis
creating value in pharmaceuticals

FILE COPY

MLG CSR 11976
11/18/2021
Robin Hagy
**Exh. 9**

November 6, 2009

**UPS OVERNIGHT COURIER**

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

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

Dear Sir/Madam:

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

KADIAN – Reprint
Material Code: KADI9ETOH

If you have any questions relating to this submission, please do not hesitate to contact the undersigned at (908) 659-3017.

Sincerely,

**ACTAVIS ELIZABETH LLC**

Francesca Procaccia /for
Lucy Gary
Manager, Regulatory Affairs,
Labeling & Graphics

/cg
Enclosures

PLAINTIFFS TRIAL EXHIBIT
**P-21965_00001**

EXHIBIT 13
Hagy
11/13/19
Reported by: Emily Samelson, CSR 14043

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

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

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

1. DATE SUBMITTED: 11/06/2009

2. LABEL REVIEW NO. (Biologics)

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

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

4. PROPRIETARY NAME: KADIAN

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

6. PACKAGE INSERT DATE and ID NO. (Latest final printed labeling): Rev. February 2009 Part# 40-9101

7. MANUFACTURER NAME:
License No. (Biologics)

**FDA/CBER USE ONLY**

| REVIEWED BY | DATE | RETURNED BY | DATE |
|---|---|---|---|
| | | | |

8. **ADVERTISEMENT / PROMOTIONAL LABELING MATERIALS**

Please check only one: X Professional  Consumer

| Material Type (use FDA codes) a. | Dissemination/ Publication Date b. | Applicant's Material ID Code and/or description c. | Previous review No. if applicable / date (PLA Submissions) d. | COMMENTS: |
|---|---|---|---|---|
| PRP | November 2009 | KADIAN - Reprint (KADI9ETOH) | N/A | |
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Add Continuation Page

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Lucy Gary
Manager, Regulatory Affairs, Labeling & Graphics

10. SIGNATURE OF RESPONSIBLE OFFICIAL: Francesca Prisciotta /for

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

12. RESPONSIBLE OFFICIAL'S
a. PHONE NO.
(908) 659-3017
b. FAX NO.
(909) 659-2250

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

*Reprinted from*
Volume 9, Number 4
April 2008


The Journal of Pain
OFFICIAL JOURNAL OF THE AMERICAN PAIN SOCIETY

# Effect of Concomitant Ingestion of Alcohol on the In Vivo Pharmacokinetics of KADIAN (Morphine Sulfate Extended-Release) Capsules

Franklin Johnson, George Wagner, Stephen Sun, and Joseph Stauffer

American Pain Society

www.jpain.org
www.sciencedirect.com

The KADIAN shell is composed of a combination of pH-independent and pH-dependent water-soluble polymers interspersed within a water-insoluble polymer matrix. This unique combination results in pH-dependent drug release from KADIAN. Although the exact mechanism is not well understood, the poor solubility of the pH-dependent polymer, methacrylic acid copolymer, at low pH, may offer sufficient protection from coingested alcohol while the capsule is in the stomach, where alcohol would be quickly absorbed. The copolymer then gradually dissolves with increasing pH as the capsule moves from the stomach through the GI tract to release the morphine sulfate.

While KADIAN maintained its extended-release profile after co-ingestion with alcohol, consumption of alcohol with any morphine product, whether immediate- or extended-release, is not recommended. All opioids, including KADIAN, may be expected to have additive effects and potentially serious outcomes when used in conjunction with alcohol, other opioids, or illicit drugs that cause CNS depression.[4]

In calling for careful evaluation of the potential for dose-dumping with extended-release dosage forms, the FDA acknowledged that product labeling and other means of informing patients about potential drug-alcohol interactions may not always be effective. The development of extended-release formulations that are not sensitive to alcohol is a goal.[6] Further investigations of social drinking and prolonged moderate alcohol intake may clarify the potential for drug interactions when extended-release formulations are ingested with alcohol.

KADIAN is a registered trademark. KADIAN is a trademark owned by Alpharma Pharmaceuticals LLC. All other brand names are the property of their respective owners.

## Acknowledgments

Technical expertise was provided by Alfred Liang, Alpharma Pharmaceuticals LLC. Writing and editorial support for this manuscript was provided by Innovex Medical Communications, Parsippany, NJ.

## References

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

LTR 1 OF 1

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

**MD 207 9-59**

**UPS NEXT DAY AIR** **1**
TRACKING #: 1Z 062 077 01 9028 2111

BILLING: P/P

Reference#1: DDMAC - Kadian

US 11.8.03 W3F2860 96.0A 10/2009

TM

# Proof of Delivery

Dear Customer,

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

| | |
|---|---|
| **Tracking Number:** | 1Z0620770190282111 |
| **Reference Number(s):** | DDMAC - KADIAN |
| **Service:** | NEXT DAY AIR |
| **Shipped/Billed On:** | 11/06/2009 |
| **Delivered On:** | 11/09/2009 8:34 A.M. |
| **Delivered To:** | 5901B AMMENDALE RD<br>BELTSVILLE, MD, US 20705 |
| **Signed By:** | YOUNG |
| **Location:** | RECEIVER |

Thank you for giving us this opportunity to serve you.

Sincerely,

UPS

Tracking results provided by UPS: 11/09/2009 10:40 A.M. ET