# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number: NDA 20-616/S-001**

**Trade Name:Kadian Sustained Release Capsules 20 mg, 50 mg and 100 mg**

**Generic Name:(morphine sulfate)**

**Sponsor: F.H. Faulding and Company Limited**

**Approval Date: July 29, 1997**

**Indication: Provides for an alternate method of administration of the pellets contained in the Kadian capsules for patients who have difficulty swallowing whole capsules**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION: NDA 20-616/S-001

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| | Included | Pending Completion | Not Prepared | Not Required |
|---|---|---|---|---|
| Approval Letter | X | | | |
| Tenative Approval Letter | | | | X |
| Approvable Letter | | | X | |
| Final Printed Labeling | | X | | |
| Medical Review(s) | X | | | |
| Chemistry Review(s) | X | | | |
| EA/FONSI | | | X | |
| Pharmacology Review(s) | | | X | |
| Statistical Review(s) | | | X | |
| Microbiology Review(s) | | | X | |
| Clinical Pharmacology Biopharmaceutics Review(s) | X | | | |
| Bioequivalence Review(s) | | | X | |
| Administrative Document(s) | X | | | |
| Correspondence | X | | | |

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number: NDA 20-616/S-001**

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-616/S-001

JUL 29 1997

F.H. Faulding and Company Limited
US Agent - Zeneca Pharmaceuticals
1800 Concord Pike, P.O. Box 15437
Wilmington, Delaware 19850-5437

Attention: Gerald L.Limp
Manager, Marketed Products Group
Drug Regulatory Affairs Department

Dear Mr. Limp:

Please refer to your supplemental new drug application dated January 27, 1997, received January 29, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kadian (morphine sulfate) Sustained Release Capsules, 20 mg, 50 mg and 100 mg.

We acknowledge receipt of your submission dated May 22, 1997. The User Fee goal date for this application is July 29, 1997.

The supplemental application provides for an alternate method of administration of the pellets contained in the Kadian capsules for patients who have difficulty swallowing whole capsules.

We have completed the review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-616/S-001. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-

up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Bonnie McNeal, Project Manager, at (301) 443-3741.

Sincerely,

/S/

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 20-616/S-001
HFD-170/Div. files
HFD-170/CSO/B.McNeal/Moody B.Mc 7/29/97
HFD-170/Doddapaneni/Chang-Qing Li – CW 7/29/97 DStark 7/29/97
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)

Drafted by: BmcNeal/July 25, 1997/N/cso/bonnie/n20616s1.apr
R/D Init. by: cpmoody/728/97, cjw for CQL/7/29/97, sd/7/29/97
F/T by: cs/7/29/97

APPROVAL (AP)

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-616/S-001

## MEDICAL REVIEW(S)

JUL 11 1997

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

# MEDICAL OFFICER REVIEW

**NDA#: 20,616**
**SPONSOR**: Faulding Pharmaceutical Co. and Zeneca Pharmaceuticals
**DRUG**: Kadian (Sprinkles)
**TYPE OF SUBMISSION: Labeling Supplement**
**INDICATION: MODERATE TO SEVERE PAIN**
**MEDICAL OFFICER**: Chang Q. Li, MD, Dr.PH, MSHA
**PEER MEDICAL OFFICER:** Celia Winchell, MD
**LETTER DATE BY SPONSOR:** 01/27/97
**DATE RECEIVED BY CDER:** 01/29/97
**DATE REVIEW COMPLETED:** 07/11/97
**REGULATORY ACTION: Approval Recommended**
**CSO:** Bonnie McNeal

**Study Title: Kadian Bioavilability Study (MOR-21/96)**

## Clinical Rationale for Alternative Route of Administration

Kadian (Capsules) is a formulation of sustained-release pellets of morphine sulfate, and it is given every 12 hours or 24 hours. The drug was approved by FDA in 1996 for use in patients with chronic, moderate-to-severe pain who require repeated dosing with a potent opioid analgesic.

The dosage and administration guidelines in the current labeling for Kadian clearly states that Kadian capsules should be swallowed whole and the capsules and pellets must not be chewed, crushed, dissolved or mixed with food. This is an appropriate means of administering Kadian to the vast majority of patients. However, there are chronic cancer pain patients and others who cannot swallow tablets or capsules.

The purpose this submission is to propose a labeling change which provides an alternative method of administration of the pellets contained in the Kadian capsules for patients who have difficulty in swallowing whole capsules. The method is to sprinkle the pellets onto soft food as the polymer-coated pellet delivery system allows the option of opening the capsules.

## KADIAN Delivery System

Kadian capsules are composed of a hard gelatin capsule containing identical pellets. The pellets or coated cores act as reservoirs for morphine sulfate. The pellet cores are surrounded by a dissolution-controlling polymer membrane which controls the rate of release of morphine sulfate. The polymer coating consists of:

- an insoluble polymer component (ethylcellulose)
- an enteric polymer component (methacrylic acid copolymer which is insoluble and relatively hydrophobic at pH 1.2)
- a water soluble component (polyethylene glycol, which is soluble and hydrophilic at pH 1.2)
- a water insoluble plasticizer (diethyl phthalate).

At a pH of 1.2, which approximates that of the human stomach, the hydrophilic component of the coating dissolves and allows water to diffuse into the core containing morphine sulfate. Some morphine sulfate begins to dissolve and diffuses out through the coating. The dissolution profile is essentially linear at this pH.

At a higher pH which approximate that of the human small intestine, both the hydrophilic and enteric components of the coat dissolve. Thus, the rate of dissolution of morphine sulfate from the core increases as the pH increases until maximal release occurs at a pH of 7.0 - 7.5.

The Kadian delivery system releases morphine sulfate significantly more slowly than immediate release morphine sulfate tablets and shorter-acting controlled-release oral morphine sulfate preparations. Although the extent of absorption of morphine following oral administration of immediate release tablets and sustained release formulations are essentially the same, the time to peak blood levels ($T_{max}$) will be longer for formulations which delay the release of morphine in the gastrointestinal tract.

Kadian has three capsule strengths available, 20 mg, 50 mg and 100 mg, each containing identical pellets. The different numbers of pellets in each of the 3 capsules is used to control the dosage strength.

The pharmacokinetic and pharmacodynamic profiles of Kadian have shown that Kadian is clinically effective as an analgesic for 24 hours if the total daily morphine requirement is given once a day. The labeling change is supported by a bioavailability study.

## Kadian Bioavilability Study in Human Healthy Volunteers (MOR-21/96)

*Study Design* The bioavailability and kinetic profile of KADIAN were compared after administration of a whole capsule or the contents of the capsule (pellets) sprinkled on applesauce. The study used a randomized, open-label, single dose, four treatment, four

period crossover design in healthy volunteers with all treatment periods separated by a 7 day washout period.

*Subject Summary* Twenty-eight (28) healthy adult volunteers, who complied with the inclusion/exclusion criteria stated in the Protocol, were selected to participate in the trial. However, one subject did not present at Period 1 check-in resulting in 27 healthy subjects (21 males and 6 females) being enrolled in the trial and dosed in Period 1. Male subjects were aged years (mean 24 years, median 22 years). Female subjects were aged years (mean 24 years, median 23 years). One subject was withdrawn during check-in of trial Period 3 after testing positive for cannabinoids in urine, resulting in 26 subjects completing all four trial periods.

*Results* The results from this volunteer trial demonstrated that pellets of KADIAN sprinkled on applesauce were shown to be roughly bioequivalent to KADIAN capsules swallowed whole in both fed and fasted conditions (See detailed PK review by Dr. Doddapaneni).

*In vitro* data submitted by the sponsor cannot be used for evaluation because the dissolution method used was different from the original NDA method. Therefore, it cannot assess the release characteristics of morphine from the pellets in various food substances, and the administration of morphine pellets via a nasogastric and gastrostomy tube under laboratory conditions.

*Safety* No serious adverse events were reported. Adverse events experienced under the different treatment conditions were similar. A total of 176 possible morphine-related adverse events occurred. AE rates and drug-related adverse events are summarized in Table 1 and Table 2.

**Table 1. Adverse Events (Protocol No. MOR-21-/96)**

| | TREATMENT A | TREATMENT B | TREATMENT C | TREATMENT D |
|---|---|---|---|---|
| TOTAL NUMBER OF SUBJECTS | 27 | 27 | 26 | 26 |
| NUMBER OF SUBJECTS WITH ONE OR MORE ADVERSE EVENTS | 18 (66.7%) | 17 (63.0%) | 16 (61.5%) | 20 (76.9%) |
| NUMBER OF SUBJECTS WITH ADVERSE EVENTS | | | | |
| Body as a Whole | 8 (29.6%) | 5 (18.5%) | 8 (30.8%) | 8 (30.8%) |
| Cardiovascular System | 3 (11.1%) | 6 (22.2%) | 5 (19.2%) | 4 (15 4%) |
| Digestive System | 9 (33.3%) | 5 (18.5%) | 6 (23.1%) | 6 (23.1%) |
| Endocrine System | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Hem and Lymphatic System | 3 (11.1%) | 2 (7.4%) | 2 (7.7%) | 1 (3.8%) |
| Metabolic and Nutritional Disorder | 1 (3.7%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Musculoskeletal System | 0 (0%) | 1 (3.7%) | 1 (3.8%) | 0 (0%) |
| Nervous System | 8 (29.6%) | 11 (40.7%) | 8 (30.8%) | 13 (50.0%) |
| Respiratory System | 7 (25.9%) | 6 (22.2%) | 5 (19.2%) | 7 (26.9%) |
| Skin and Appendages | 1 (3.7%) | 2 (7.4%) | 1 (3.8%) | 2 (7.7%) |
| Special Senses | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Urogenital System | 1 (3.7%) | 0 (0%) | 0 (0%) | 0 (0%) |

Treatment A: 1x50mg Kadian capsule, contents sprinkled over apple sauce and administered after an overnight fast of at least 10 hours
Treatment B: 1x50mg Kadian capsule, swallowed whole with apple sauce after an overnight fast of at least 10 hours
Treatment C: 1x50mg Kadian capsule, contents sprinkled over apple sauce and administered immediately following a standard, high-fat content breakfast
Treatment D: 1x50mg Kadian capsule, swallowed whole with apple sauce immediately follow a standard, high-fat content breakfast

**Table 2. Summary of Drug-Related Adverse Events (MOR-21/96)**

| BODY SYSTEM | Description | Kadian Sprinkle Fasted | Kadian Whole Fasted | Kadian Sprinkle Fed | Kadian Whole Fed |
|---|---|---|---|---|---|
| Nervous System | Drowsiness | 1 | 4 | 4 | 4 |
| | Dizziness | 10 | 4 | 4 | 6 |
| | Lethargic | 1 | 1 | 0 | 0 |
| | Uncoordinated | 0 | 1 | 0 | 1 |
| | Vagueness | 0 | 4 | 0 | 1 |
| Respiratory System | Hiccup | 1 | 0 | 4 | 2 |
| Digestive System | Nausea | 8 | 7 | 6 | 6 |
| | Vomiting | 5 | 1 | 1 | 2 |
| | Constipation | 1 | 0 | 2 | 0 |
| Body as a whole | Headache | 4 | 3 | 5 | 4 |
| | Abdominal pain/discomfort | 1 | 0 | 0 | 1 |
| | Tiredness | 2 | 3 | 1 | 2 |
| | Back pain | 1 | 1 | 1 | 1 |
| | Chills and fever | 0 | 0 | 0 | 2 |
| Cardiovascular System | Hypotension | 5 | 10 | 10 | 7 |
| | Faint | 0 | 2 | 0 | 0 |
| Skin and Appendages | Itchiness | 1 | 1 | 1 | 2 |
| Miscellaneous | | 3 | 2 | 2 | 6 |
| **Total** | | **44** | **44** | **41** | **47** |

**Conclusions**

Pellets of Kadian sprinkled on applesauce were bioequivalent to Kadian capsules swallowed whole under fasting conditions. The relationship between the blood level of morphine and the analgesic response is complex, and it depends on the patient's age, state of health, medical condition, and the extent of previous opioid treatment. However, the two Kadian administration methods with similar pharmacokinetic parameters may be expected to be therapeutically equivalent under the same treatment condition.

Safety profiles of Kadian sprinkled on applesauce are similar to Kadian capsules swallowed whole in the tested population. Kadian Capsules with its polymer-coated pellet delivery system can be administered by the sprinkled method among adult patients who cannot swallow tables or capsules.

There is insufficient evidence that morphine pellets can be administered on other food substances or via a nasogastric and gastrostomy tube.

There is the lack of evidence that it is appropriate to divide up the applesauce for pediatric use. The safety and effective use of Kadian, both the entire capsule and the pellets sprinkled on applesauce, have not been directly investigated in pediatric patients below the age of 18 years. There are studies from the literature reporting the safe use of oral morphine preparations for analgesia in pediatric patients who were dosed on a per kilogram basis. However, the doses available for this product (20 mg, 50 mg, and 100 mg) might be high relative to the expected requirement of small pediatric patients. It is our concern that some pediatricians might think that the applesauce Kadian sprinkles is an easy way for the drugs to be administered in pediatric patients. Therefore, the new label should clearly indicate that the applesauce sprinkling method is **NOT** an appropriate alternative for these patients at present.

**REGULATORY ACTION:**

- **Approval Recommended.**
- **The label language would have to be more restrictive, stating exactly what food the product could be sprinkled into.**
- **The current KADIAN product should not used by the sprinkle method in pediatric patients who are too small to take capsules. The Agency would strongly recommend the sponsors pursue pediatric PK/PD studies if the sponsors plan to extend the line to include lower doses more appropriate for small pediatric patients.**

/S/

Chang Q. Li, MD, DrPH
Medical Review Officer

CC: Original NDA # 20,616
HFD-170 Division File
HFD-170 Chang Q Li
HFD-170 Celia Winchell
HFD-170 Bonnie McNeal
HFD-344
R/D Init. by: CWinchell/7-11-97
F/T by: sl/7-15-97

/S/

MD 7/11/97

Celia Winchell, MD
Medical Peer Review

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-616/S-001

## CHEMISTRY REVIEW(S)

MAY 17 1996
Division File

**DIVISION OF ANESTHETIC, CRITICAL CARE & ADDICITION DRUG PRODUCTS HFD-170**
**Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 20-616

**REVIEW** **DATE REVIEWED:** 5.6.96

| SUBMISSION TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|
| BC | 4-22-96 | 4-23-96 | 5-1-96 |

**NAME & ADDRESS OF APPLICANT:**
Faulding Inc, 200 Elmora Ave, Elizabeth, NJ 07207, George Wagner, Manager RA, tel 908-527-9100 ext 337.

**DRUG PRODUCT NAME**
Proprietary: KADIAN Morphine sulfate sustained release capsules, 20,50 and 100 mg.
Established: Morphine sulfate pentahydrate SR pellets in capsule.
Code Name/#: CAS# 6211-15-0.
Chem.Type/Ther.Class: 3S

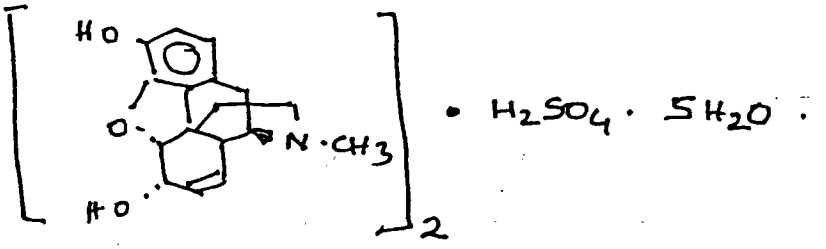
**PHARMACOL. CATEGORY:** Opioid analgesic for once a day administration.
**DOSAGE FORM:** Hard gelatin capsule containing light tan pellets.

**STRENGTHS:** 20 mg (# 4 capsule, clear cap imprinted 'KADIAN' and clear body imprinted '20' in black).
50 mg (# 2 capsule, clear cap imprinted 'KADIAN' and clear body imprinted '50' in black).
100 mg (#0 capsule, clear cap imprinted 'KADIAN' and clear body imprinted '100' in black).

**ROUTE OF ADMINISTRATION:** Oral (should not be chewed or crushed; should be swallowed).

**DISPENSED:** X Rx _____ OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:**
7,8-didehydro-4,5 (alpha)-epoxy-17-methyl-morphinan-3,6 (alpha)-diol sulfate (2:1) salt pentahydrate; molecular weight 758.85.



REMARKS:

Recommends approval of minor changes for the commercial scale: from kg to kg coated pellets batch, from print changes on capsule. process validation will be completed prior to commercial distribution.

CONCLUSIONS & RECOMMENDATIONS:

Recommends approval of minor changes in CMC section for Kadian (morphine sulfate) sustained release pellets in capsules, 20, 50 and 100 mg.

/S/

P.Maturu, PhD, Primary Review Chemist

/S/ 5/17/96 acting

A.D'Sa, PhD, Chemistry Team Leader

cc:
Orig. NDA 20-616
HFD-~~007~~/Division File
HFD-~~007~~/PMaturu, AD'Sa
HFD-~~007~~/BMcNeal, CWright, RBedford
R/D by: AD'Sa/5-17-96
filename: N20616.965
SATISFACTORY
F/T by: PO'Connor/5-17-96

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-616/S-001

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 27 1997

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

**NDA:** 20-616 **SUPPLEMENT NO.:** 001
**NAME:** KADIAN™ (Morphine Sulfate Sustained Release) Capsules
**SPONSOR:** F. H. Faulding & Co. Limited, Concord Pike, PO Box 15437, Wilmington, DE
**TYPE OF SUBMISSION:** Labeling Supplement **SUBMISSION DATE:** January 27, 1997
**REVIEWER:** Suresh Doddapaneni, Ph.D. **REVIEW DATE:** June 12, 1997

## SYNOPSIS

KADIAN™ (morphine sulfate controlled release capsules) was approved for marketing in July of 1996 in strengths of 20, 50, 100 mg for once a day treatment of moderate to severe pain where treatment with an opioid analgesic is indicated for more than a few days. The current labeling for KADIAN™ capsules directs that the capsules should not be opened, crushed, dissolved or mixed with food. The purpose of the current submission is to propose a labeling change providing alternative methods of administration of the pellets contained in these capsules for patients who have difficulty in swallowing whole capsules. These methods include either sprinkling the pellets onto soft food, mixing the pellets with liquid or administering the pellets through a gastrostomy tube. The sponsor submitted one bioavailability study and *in vitro* dissolution data in support of these labeling changes. Although, the bioavailability study supports the use of apple sauce, the *in vitro* dissolution data does not support the use of other food items tested or administering the pellets through a gastrostomy tube as the parameters of the dissolution method used were sufficiently different from what was used in the original NDA casting an uncertainty on the validity of the data.

## RECOMMENDATION

Supplement 001 to NDA 20-616 can be approved. The proposed labeling changes are not acceptable to the Agency in their current form. Labeling should be restricted to only apple sauce for which *in vivo* data is available. Sponsor should be sent the Agency's modifications.

/S/ 6/27/97
Suresh Doddapaneni, Ph.D.
Pharmacokineticist
DPE II/OCPB

RD initialed by Dale Conner, PharmD. /S/ 6/27/97
FT initialed by Dale Conner, PharmD.
CC:
NDA 20-616, HFD-170 (Division files, McNeal), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Conner), HFD-340 (Viswanathan), CDR (Barbara Murphy).

## 1.0. INTRODUCTION

KADIAN™ (morphine sulfate controlled release capsules) was approved for marketing in July of 1996 in strengths of 20, 50, 100 mg for once a day treatment of moderate to severe pain where treatment with an opioid analgesic is indicated for more than a few days. The current labeling for KADIAN™ capsules directs that the capsules should not be opened, crushed, dissolved or mixed with food. The purpose of the current submission is to propose a labeling change providing alternative methods of administration of the pellets contained in these capsules for patients who have difficulty in swallowing whole capsules. These methods include either sprinkling the pellets onto soft food, mixing the pellets with liquid or administering the pellets through a gastrostomy tube.

KADIAN™ capsules are composed of a hard gelatin capsule containing identical pellets (different number of pellets are used to make up the three strengths of 20, 50, and 100 mg). The pellet cores are surrounded by a dissolution-controlling polymer membrane consisting of an insoluble polymer component, an enteric polymer component (insoluble and relatively hydrophobic at pH 1.2), a water soluble component (soluble and hydrophilic at pH 1.2), and a water insoluble plasticizer. At a pH of 1.2 (stomach pH), the hydrophilic component dissolves allowing water to diffuse into and dissolve morphine sulfate. At a higher pH (small intestine pH), both the hydrophilic and enteric coatings dissolve with dissolution rate of morphine sulfate from the core increasing until maximal release occurring at a pH of 7.0-7.5.

This submission contains; (1) An *in vivo* bioavailability study of the effect of food on pellets sprinkled on apple sauce and whole capsules taken with apple sauce (2) An *in vitro* morphine release study after mixing the pellets with custard, yogurt, apple sauce, and strawberry jam (3) An *in vitro* morphine release study after mixing the pellets with ice cream, milk, orange juice, and water (4) *In vitro* data on the possibility of administration of the pellets through nasogastric and gastrostomy tubes.

## 2.0. BIOAVAILABILITY STUDY.

**Objectives:**

To compare the pharmacokinetic profile and relative bioavailability, under fasted and fed conditions, of kadian using two methods of dose administration.

**Principal Investigator:**

**Analytical Investigator:**

**Analytical Methodology:**

**Design:**

This was a randomized, balanced, analytically-blinded, single-dose, four-treatment, four-period crossover trial in 28 healthy adults (19 males and 6 females had evaluable data), with a one week washout period between treatments (protocol number MOR-21/96 (3394US/001)). The four treatments were;

A: 1 x 50mg Kadian capsule, contents sprinkled over apple sauce and administered under fasted conditions (pellets not chewed or crushed).

B: 1 x 50mg Kadian capsule, swallowed whole with apple sauce and administered under fasted conditions.

C: 1 x 50mg Kadian capsule, contents sprinkled over apple sauce and administered immediately following a standard, high-fat content meal (pellets not chewed or crushed).

D: 1 x 50mg Kadian capsule, swallowed whole with apple sauce and administered immediately following a standard, high-fat content meal.

One tablespoon (15 mL) of apple sauce was used in each treatment with each dose taken with 240 mL room-temperature water. The high fat meal used was similar in composition to the FDA recommended high fat meal. Seven (7) mL blood samples were collected pre-dose and at the following times after administration of each dose: 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 14, 16, 32, 40 and 48 hours post-dose.

The following pharmacokinetic parameters were calculated for the four treatments: AUC, $AUC_{inf}$, $C_{max}$, $t_{max}$, $K_{el}$, $t_{1/2}$ and width (time period for which the observed plasma concentration is greater than or equal to 75% of the maximum observed plasma concentration). ANOVA with effects for treatment, subject (sequence), period and sequence was used for statistical analysis. The two one sided t-tests procedure was used to construct 90% confidence intervals for the ratios of the test and reference log transformed parameters.

**Results and Discussion:**

Table 1 contains the results of the bioequivalency analysis on $C_{max}$ and AUC while figure 1 depicts the plasma concentration vs. time profiles of morphine for the four treatments. For the statistical analysis, the sponsor did not incorporate carry over effect in the ANOVA model. A recommendation to include this was made by the pharmacokinetic reviewer when this protocol submitted on August 2, 1996 was reviewed (IND The sponsor responded to this suggestion on March 4, 1997 justifying the exclusion of the carry over effect in the ANOVA model. Pre-dose time points showed zero concentrations and the 4-by-4 Williams Square study design employed is balanced for first order carry-over effects.

1) Sprinkle vs whole capsule under fasting conditions:

ANOVA analysis indicated that there were no statistically significant differences between the sprinkle and whole capsule LSMEANS for all pharmacokinetic parameters. The 90% confidence intervals for the log-transformed parameters $C_{max}$, AUC, and $AUC_{inf}$ were all within 80-125% limits allowed for bioequivalence. The mean $t_{max}$ was similar between the two treatments (7.86 hours and 7.38 hours for the sprinkle and whole capsules respectively).

2) Whole capsule under fed vs fasting conditions:

ANOVA analysis indicated that there were no statistically significant differences between LSMEANS under fed and fasting conditions for all parameters with the exception of $t_{max}$ and $t_{1/2}$. The 90% confidence intervals for the log transformed $C_{max}$, AUC, and $AUC_{inf}$ were all within the bioequivalency limits. The mean $t_{max}$ under fasting conditions was 7.4 hours compared with 11.6 hours under fed conditions. Correspondingly, the mean $t_{1/2}$ was slightly longer under fed conditions compared with fasting conditions (17 hours vs 15 hours). However, these changes in $t_{max}$ and $t_{1/2}$ may not be clinically important in the clinical setting where this product is chronically used in a once a day dosage regimen.

3) Sprinkle vs whole capsule under fed conditions:

ANOVA analysis indicated that between the sprinkle and whole capsule under fed conditions, there were no statistically significant differences between the LSMEANS of all parameters with the exception of $C_{max}$, width, and $LC_{max}$. The 90% confidence intervals for the log transformed AUC

and $AUC_{inf}$ were within the bioequivalency limits. For $C_{max}$, however, the interval was 77.1-93.8. The mean ratios of the log-transformed parameters were 85.0% for $C_{max}$, 97.5% for AUC and 98.1% for $AUC_{inf}$. The mean $t_{max}$ value for sprinkle was 11.6 hours, compared with 11.64 hours for the whole capsule. For $C_{max}$, which failed bioequivalency criteria, the mean ratio of the log transformed value between the sprinkle vs whole capsule was 85%. Probably, in the clinical setting of usage for this product, this may not make a difference.

4) Sprinkle under fed and fasting conditions:

ANOVA analysis indicated that under fed and fasting conditions for the sprinkle treatment, there were no statistically significant differences between the LSMEANS for all parameters with the exception of $C_{max}$, $t_{max}$, $t_{1/2}$, width and $LC_{max}$. Although the 90% confidence intervals were within the limits for log-transformed AUC and $AUC_{inf}$, the interval for $C_{max}$ was outside of the limit. The mean ratios of the log-transformed parameters were 96.7% for AUC and $AUC_{inf}$, and 79.1% for $C_{max}$. The $t_{max}$ increased from 7.86 hours under fasting conditions to 11.6 hours under fed conditions. The $t_{1/2}$ increased from 15.0 hours under fasting conditions to 16.5 hours under fed conditions. Overall, the observed reduction in the rate of morphine absorption under fed conditions, as evidenced by the decreased $C_{max}$ and lengthened $t_{max}$, resulted in a more sustained (or flattened) morphine plasma profile when compared with fasting conditions. As such, the product's clinical performance under fed conditions may still be similar to the fasting state.

This study was conducted in healthy volunteers with the 50 mg strength. Ideally, food effect study is conducted at the highest strength for a particular product. Since, the 100 mg strength of Kadian is similar to the 50 mg strength in proportions of active and inactive ingredients, similar results can be expected at the 100 mg strength.

**Table 1.** Results of the pair-wise bioequivalency comparisons (treatment means and 90% confidence intervals).

| Treatment Comparison | $C_{max}$ | $AUC_{0-48}$ | $AUC_{inf}$ |
|---|---|---|---|
| Fasting-Sprinkle vs Capsule | (11.69, 10.78)<br>97.3-119.6 | (162.23, 162.67)<br>95.1-104.3 | (187.92, 191.28)<br>93.6-102.9 |
| Capsule-Fed vs Fasting | (10.49, 10.78)<br>86.2-108.5 | (161.02, 162.67)<br>94.4-103.6 | (184.80, 191.28)<br>91.9-101.3 |
| Fed-Sprinkle vs Capsule | (9.00, 10.49)<br>74.4-97.2 | (156.49, 161.01)<br>92.5-101.9 | (180.32, 184.80)<br>92.7-102.4 |
| Sprinkle-Fed vs Fasting | (9.0,11.69)<br>66.8-87.3 | (156.49, 162.23)<br>91.8-101.1 | (180.32, 187.92)<br>91.2-100.7 |

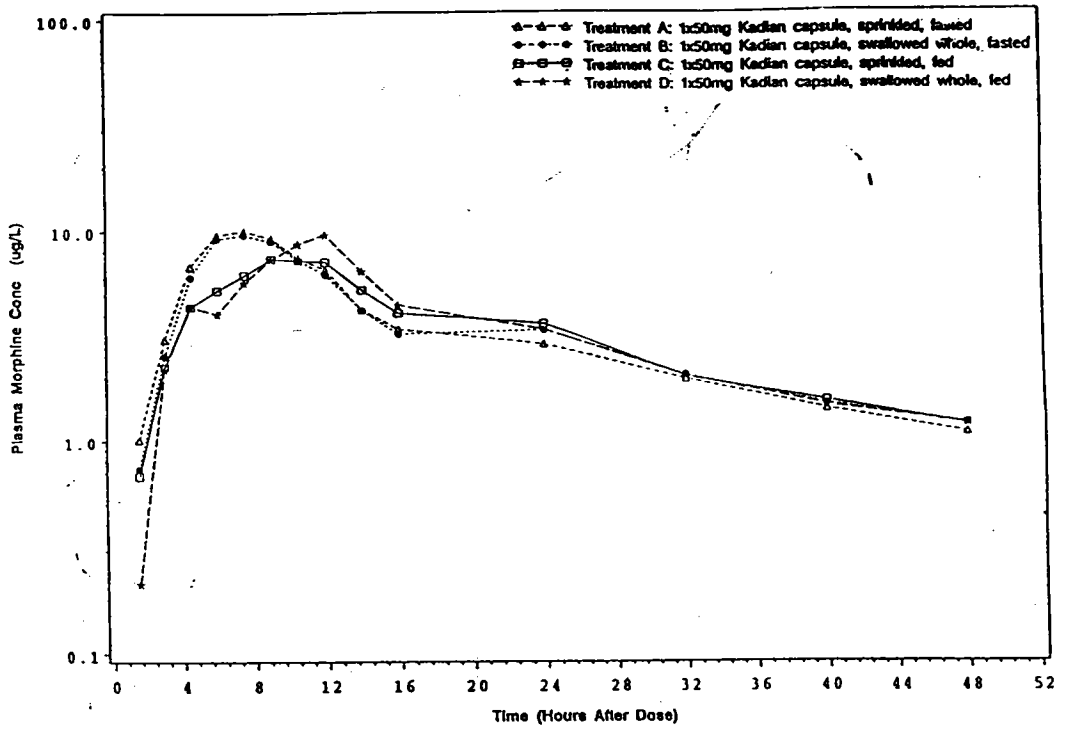



**Figure 1.** Morphine mean plasma concentration vs time profiles of the capsule and sprinkle under fed and fasting conditions.

## Conclusions

1. Kadian capsule contents sprinkled over apple sauce, and Kadian capsules swallowed whole with apple sauce were bioequivalent when administered under fasting conditions.
2. Kadian capsules swallowed whole with apple sauce were bioequivalent when given under fasted and fed conditions.
3. Kadian capsule contents sprinkled over apple sauce and kadian capsules swallowed whole with apple sauce were bioequivalent with respect to AUC under fed conditions. However, $C_{max}$ barely failed the bioequivalency criteria and as such its clinical performance may be expected to be the same.
4. Kadian capsule contents sprinkled over apple sauce were not bioequivalent when given under fasted and fed conditions. However, the reduction in $C_{max}$ observed with food may not be clinically significant for kadian which is a sustained-release morphine formulation designed for chronic once-a-day dosing.

## 3.0. *IN VITRO* DRUG RELEASE PROFILES.

In addition to the bioavailability study conducted with apple sauce, the sponsor used *in vitro* dissolution testing to explore the use of other food items such as custard, apple sauce, yogurt, strawberry jam, ice cream, orange juice, milk, and water as well as nasogastric and gastrostomy tubing for administering the pellets. The drug release testing methodology used for this purpose was different from that used in the original NDA. However, the specifications used were identical to that used for the product release and expiry testing of kadian pellets in the original NDA. In the original NDA, the dissolution testing utilized USP apparatus 1 (basket) at 100 RPM, acid stage 500 mL 0.1N HCL for 1 hour followed by 500 mL phosphate buffer pH 7.5 for 7 hours. In the current supplement, the dissolution testing was done at 50 RPM and the acid stage was completely omitted (dissolution testing was done in 500 mL pH 7.5 phosphate buffer for 7 hours only). The implication of the reduced basket speed and omission of the acid stage is that the pellets are now subjected to mild dissolution conditions and as such any effect of food would not be revealed unless it is a dramatic effect. The fact that control pellets passed the specifications under the new conditions still does not rule out the protective effect the new conditions had on the food treated pellets. These concerns were communicated to the sponsor in a telecon held on April 10, 1997. The sponsor responded that the Agency continue reviewing the current labeling supplement as submitted and the issue of performing additional *in vitro* tests with soft food and liquids using the methodology cited in the NDA will be considered in the future. As such, the *in vitro* dissolution data submitted in support of the use of above mentioned food items as well as nasogastric and gastrostomy tubing will not be reviewed and statements proposed by the sponsor in the package insert regarding these would be disallowed.

## 4.0. OVERALL CONCLUSIONS

1. The bioavailability study supports the proposed labeling change of allowing the pellets to be sprinkled on apple sauce.
2. The *in vitro* dissolution data was collected using a modification of the dissolution method used in the original NDA. Although the control pellets met the specifications, one cannot be sure if the test pellets would have passed the specifications using the original method. Since the sponsor chose not to submit new data using the original method, any references to conclusions drawn from this data would not be allowed to be made in the package insert.

## 5.0. PROPOSED LABELING CHANGES

The labeling changes proposed by the sponsor are given below (strike out's are reviewer proposed changes);

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Redacted 2

pages of trade

secret and/or

confidential

commercial

information

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-616/S-001

## ADMINISTRATIVE DOCUMENTS

~~AUG 7 1997~~ (A)
AUG 5, 1997
AUG 5 1997

# CSO Review of Labeling

**NDA 20-616**

**Drug: Kadian (morphine sulfate tablets)**
**Sponsor: Faulding Services Inc.**

Materials Reviewed:
The final printed package insert ( marked with the identification numbers 64093-01, 40-8912, Rev G 07/96) was submitted on November 15, 1996. This was compared to the approved labeling, which was issued with the approval letter of the NDA on July 3, 1996.

Conclusions:

The submitted final labeling is identical to the July 3, 1996 approved labeling with the following exceptions.

1. At the end of the paragraph under graph #1, the words were bolded. This change is acceptable as it is should have been bolded in the original version.

2. The same was done with the words at the end of the pediatric section. This also conforms with the format of the rest of the label.

3. At the end of the section, the words were bolded. This is also acceptable.

4. Under the first sentence reads The word should be replaced with the plural This error was in the approved version and should be corrected.

5. Under , a comma was added after This had been left out in error in the approved version.

6. Under the word in the second paragraph was not bolded. Checked with Dr. Chang-Qing Li, who would like to see this word bolded.

7. Under the word (breakthrough pain) had the surrounding single quote marks removed. This change was acceptable to the medical officer, Dr. Li.

8. Under

, small letters in the approved version were correctly changed to capitals.

9. Under , small letters in the approved version were correctly changed to capitals.

10. Changes were made under the section to the NDA numbers for bottles of 60 of each of the different strengths of tablets. For example was changed to I assume the sponsor corrected the original version of the labeling.

In summary, all changes to the labeling are acceptable except for item #6 above. The word should be bolded. Also, the error noted in #4 should be corrected in the next printing of the label.

/S/ 7/17/97

Bonnie McNeal
Project Manager

Concur: /S/ 7/17/97

Corinne P. Moody
Chief, Project Management Staff

cc:
orig NDA 20-616
Div File
HFD-170/BMcNeal

DF

# MEMORANDUM OF TELECON

NDA: 20-616/S-001

SPONSOR: Faulding Inc.

DATE: April 10, 1997 9:00AM

SUBJECT: Bioequivalency and Dissolution Data in NDA Supplement 001

BETWEEN: Dr. Bruce Birmingham, Metabolism, Zeneca
George Wagner, Regulatory, Faulding

and Dr.Suresh Doddapaneni, Biopharmaceutics Reviewer
Dr. Dale Conner, Biopharmaceutics Supervisor
and Bonnie McNeal, Project Manager of HFD-170/FDA

The sponsor has provided a bioequivalence study for using Kadian pellets sprinkled onto applesauce. They have also provided in vitro dissolution data for applesauce and a number of other foods.

The agency, however, has concerns about the methods used for the dissolution studies. The methods used for the current supplement are not the same as those used in the original NDA. Therefore, the agency feels that this data may not be reliable. The sponsor could repeat the studies using the same methods as those used in the original NDA.

The agency is comfortable labeling the sprinkled pellets in applesauce, provided the bioequivalence study data is acceptable. The agency is not comfortable using the drug with other foods with existing data.

The sponsor was given 3 options:

1) They could use only applesauce in the label if the bioequivalence study is ok, and not pursue other options.
2) They can generate fresh in vitro dissolution data with the method used in the original NDA before the PDUFA date and agency can evaluate it based on the quality of data and precedence from the past. The agency must look into whether in vivo studies are usually required in a situation like this.
3) The sponsor could accept labeling with applesauce now and come back later with a new supplement to expand the use in other foods.

The sponsor will look into the options and contact the agency at a later date.

**See Attachment: "Notes for the Telecon with Faulding 4/10/97", prepared by Dr. Doddapaneni.**

**cc: NDA 20-616/S-001**
**Div. Files**
**HFD-170/McNeal/SDoddapaneni/DConner**

**Filename: kadian.tel**
**Edited by S.D. 7/9/97; D.C. 7/9/97**

# Notes for Telecon with Faulding on 4/10/97

- **Drug Release at Expiry Specifications (% of Label Claim)**

| | |
|---|---|
| 2 hours | not more than 27% |
| 4 hours | 43-65% |
| 6 hours | 69-92% |
| 8 hours | not less than 90% |

- **Dissolution Method used to set the above specifications in the original NDA**

-USP XXII apparatus 1 (basket method) at 100 RPM.
-acid stage (0.1 N HCL- pH 1.2) for 1 hour.
-alkaline stage (phosphate buffer- pH 7.5) for 7 hours.

- **Dissolution Method used in the sprinkle supplement but with the above specifications**

-Same as above except no acid stage and 50 RPM
-Has the effect of protective conditions on the food treated pellets.
-Although control pellets did pass the specifications, may not mean that the food treated pellets would have under the old conditions.

- **Data used for the proposed labeling changes**

-Apple sauce - bioequivalency study as well as *in vitro* dissolution data.
-Custard, yogurt, strawberry jam, Ice Cream, Orange Juice, Fresh Milk, and administration with Gastrostomy Tubing-Only *in vitro* dissolution data.

- **Solutions**

If the sponsor's explanation is inadequate then
(1) Use only apple sauce in the label if the bioequivalency study holds up, and the sponsor does not wish to pursue further on other food items.
(2) The sponsor can generate fresh *in vitro* dissolution data with the original method before the PDUFA date.
(3) Come back with a new supplement at a later time with apple sauce approved now.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-616/S-001

## CORRESPONDENCE

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437



CERTIFIED MAIL
RETURN RECEIPT REQUESTED

JAN 27 1997

NDA NO. 20-616 REF. NO. S-021
NDA SUPPL FOR SLR

Curtis Wright, M.D.
Acting Division Director
Division of Anesthetics, Critical Care,
and Addiction Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 170, Room No. 9B-23
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Wright:

Re: KADIAN™ (morphine sulfate sustained release) Capsules
NDA 20-616
Labeling Supplement

We take this opportunity to supplement the current approved labeling for KADIAN™ (morphine sulfate sustained release) Capsules as provided under 21 CFR 314.7(b)(3). The current labeling for KADIAN Capsules provides information on the safe and effective use of KADIAN Capsules for the management of moderate to severe pain where treatment with an opioid analgesic is indicated for more than a few days. In addition, the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the labeling direct that the capsules should not be opened, crushed, dissolved or mixed with food.

The purpose of this submission is to propose a labeling change which provides alternative methods of administration of the pellets contained in the KADIAN Capsules for patients who have difficulty swallowing whole capsules. These methods include either sprinkling the pellets onto soft food, mixing the pellets with liquid or administering the pellets through a gastrostomy tube. The labeling changes are supported by a bioavailability study and ***in vitro*** dissolution data.

ORIGINAL

Please find as Tab A (in Volume 1) the proposed labeling, created as a 3-column review document, which clearly illustrates the changes in labeling information. The left column represents the current approved labeling, the middle column represents the proposed revisions for the food sprinkling, the right column contains supporting comments (annotated).

The justification to support this labeling change is provided as follows:

Tab B (Volume 1) - Clinical Rationale for the Labeling Supplement

Tab C (Volume 1) - *In vitro* Dissolution Data

Tab 3 - Technical Memorandum No.TM92/003
Tab 7 - Technical Memorandum No.TM95/007
Tab 13 - Technical Memorandum No.TM94/013

Tab D (Volumes 2-8) - Morphine Bioavailability Study No. MOR-21/96 (3394US/001)

Please note that the *in vitro* Dissolution Data were generated by Zeneca has been granted authorization from to use this information in this submission.

We believe the supporting documentation provides adequate basis for this labeling change. If you have any questions or comments, please do not hesitate to contact me.

Sincerely,

Gerald L. Limp
Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-8017
(302) 886-2822 (fax)

GLL/DPC/jr

Desk Copy: Ms. Elizabeth T. McNeal, HFD No. 170 (Cover Letter Only)