CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-531/S-010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-531/S-010

King Pharmaceuticals, Inc
Attention: Dean R. Cirotta, MBA
Senior Director, Regulatory Affairs
501 Fifth Street
Bristol, Tennessee 37620

Dear Mr. Cirotta:

Please refer to your supplemental new drug application dated February 8, 2001, received February 14, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tigan® (trimethobenzamide hydrochloride) Capsules, 300 mg.

This supplemental new drug application provides for the following in response to the Federal Register notice of January 9, 1979, classifying this drug effective for postoperative nausea and vomiting and nausea associated with gastroenteritis: draft labeling, results of bioavailability studies, and updated manufacturing and controls and testing procedures.

We have completed the review of this supplemental application, and it is approved. This action approves this application on the basis of effectiveness of the drug as well as safety. This action also approves those supplemental applications that were permitted under the provisions of 21 CFR 314.70 and have not been superceded.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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 "FPL for approved supplement NDA 17-531/S-010." Approval of this submission by FDA is not required before the labeling is used.

The agreed upon approved dissolution specifications are listed below:

Apparatus:	USP Apparatus I (baskets) rotated at 100 rpm
Dissolution medium:	900 ml of water at 37±0.5° C
Proposed specification:	NLT(b)((Q) is dissolved in 30 minutes.

NDA 17-531/S-010

We remind you of your post marketing study commitment dated November 8, 2001, as listed below:

1. Provide additional information regarding the metabolic fate of trimethobenzamide for labeling purposes.

Please submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

We also note your agreement to circulate a "Dear Health Care Professional" letter to alert the healthcare community about the new 300 mg capsule strength. We also request that you submit a copy of the final letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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, call Melaine Shin, R.Ph., Project Manager, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}
Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-531/S-010

FINAL PRINTED LABELING

NDA 17-531/S-010

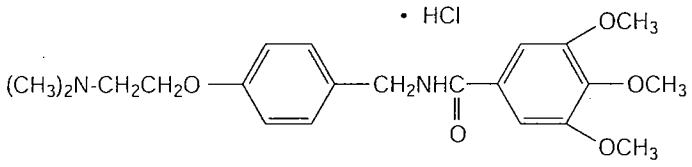
Tigan®

(trimethobenzamide hydrochloride)

Capsules/Suppositories/Injectable

DESCRIPTION

Chemically, trimethobenzamide HCl is N-[*p*-[2-(dimethylamino)ethoxy]benzyl]-3,4,5-trimethoxybenzamide monohydrochloride. It has a molecular weight of 424.93 and the following structural formula:



Capsules: Each 300-mg *Tigan*® capsule for oral use contains trimethobenzamide hydrochloride equivalent to 300 mg. The capsule has an opaque purple cap marked "Tigan" and an opaque purple body marked "M079".

Inactive Ingredients: D&C Red No. 28, FD&C Blue No. 1, lactose, magnesium stearate, starch and titanium dioxide.

Suppositories (200 mg): Each suppository contains 200 mg trimethobenzamide hydrochloride and 2% benzocaine in a base compounded with polysorbate 80, white beeswax and propylene glycol monostearate.

Suppositories, Pediatric (100 mg): Each suppository contains 100 mg trimethobenzamide hydrochloride and 2% benzocaine in a base compounded with polysorbate 80, white beeswax and propylene glycol monostearate.

Ampuls: Each 2-mL ampul contains 200 mg trimethobenzamide hydrochloride compounded with 0.2%

parabens (methyl and propyl) as preservatives, 1 mg sodium citrate and 0.4 mg citric acid as buffers and pH adjusted to approximately 5.0 with sodium hydroxide.

Multi-Dose Vials: Each mL contains 100 mg trimethobenzamide hydrochloride compounded with 0.45% phenol as preservative, 0.5 mg sodium citrate and 0.2 mg citric acid as buffers and pH adjusted to approximately 5.0 with sodium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of *Tigan*® as determined in animals is obscure, but may involve the chemoreceptor trigger zone (CTZ), an area in the medulla oblongata through which emetic impulses are conveyed to the vomiting center; direct impulses to the vomiting center apparently are not similarly inhibited. In dogs pretreated with trimethobenzamide HCl, the emetic response to apomorphine is inhibited, while little or no protection is afforded against emesis induced by intragastric copper sulfate.

Pharmacokinetics

The pharmacokinetics of trimethobenzamide have been studied in healthy adult subjects. Following administration of 200 mg (100 mg/mL) Tigan I.M. injection, the time to reach maximum plasma concentration (T_{max}) was about half an hour, about 15 minutes longer for Tigan 300 mg oral capsule than an I.M. injection. A single dose of Tigan 300 mg oral capsule provided a plasma concentration profile of trimethobenzamide similar to Tigan 200 mg I.M. The relative bioavailability of the capsule formulation compared to the solution is 100%. The mean elimination half-life of trimethobenzamide is 7 to 9 hours.

Special Populations

Gender

Systemic exposure to trimethobenzamide was similar between men (N=40) and women (N=28).

Race

Pharmacokinetics appeared to be similar for Caucasians (N=53) and African Americans (N=12).

INDICATIONS

Tigan® is indicated for the treatment of postoperative nausea and vomiting and for nausea associated with gastroenteritis.

CONTRAINDICATIONS

Use of the injectable form of *Tigan*® in children, the suppositories in premature or newborn infants, and use of any dosage form in patients with known hypersensitivity to trimethobenzamide are contraindicated. Since the suppositories contain benzocaine they should not be used in patients known to be sensitive to this or similar local anesthetics.

WARNINGS

Caution should be exercised when administering *Tigan*® to children for the treatment of vomiting. Antiemetics are not recommended for treatment of uncomplicated vomiting in children and their use should be limited to prolonged vomiting of known etiology. There are three principal reasons for caution:

1. The extrapyramidal symptoms which can occur secondary to *Tigan*® may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g., Reye's syndrome or other encephalopathy.
2. It has been suspected that drugs with hepatotoxic potential, such as *Tigan*®, may unfavorably alter the course of Reye's syndrome. Such drugs should therefore be avoided in children whose signs and symptoms (vomiting) could represent Reye's syndrome.

Tigan® may produce drowsiness. Patients should not operate motor vehicles or other dangerous machinery until their individual responses have been determined.

Usage in Pregnancy: Trimethobenzamide hydrochloride was studied in reproduction experiments in

rats and rabbits and no teratogenicity was suggested. The only effects observed were an increased percentage of embryonic resorptions or stillborn pups in rats administered 20 mg and 100 mg/kg and increased resorptions in rabbits receiving 100 mg/kg. In each study these adverse effects were attributed to one or two dams. The relevance to humans is not known. Since there is no adequate experience in pregnant or lactating women who have received this drug, safety in pregnancy or in nursing mothers has not been established.

Usage with Alcohol: Concomitant use of alcohol with *Tigan*® may result in an adverse drug interaction.

PRECAUTIONS

During the course of acute febrile illness, encephalitides, gastroenteritis, dehydration and electrolyte imbalance, especially in children and the elderly or debilitated, CNS reactions such as opisthotonos, convulsions, coma and extrapyramidal symptoms have been reported with and without use of *Tigan*® (trimethobenzamide hydrochloride) or other antiemetic agents. In such disorders caution should be exercised in administering *Tigan*®, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). Primary emphasis should be directed toward the restoration of body fluids and electrolyte balance, the relief of fever and relief of the causative disease process. Overhydration should be avoided since it may result in cerebral edema. The antiemetic effects of *Tigan*® may render diagnosis more difficult in such conditions as appendicitis and obscure signs of toxicity due to overdosage of other drugs.

ADVERSE REACTIONS

There have been reports of hypersensitivity reactions and Parkinson-like symptoms. There have been instances of hypotension reported following parenteral administration to surgical patients. There have been reports of blood dyscrasias, blurring of vision, coma, convulsions, depression of mood, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, muscle cramps and opisthotonos. If these

occur, the administration of the drug should be discontinued. Allergic-type skin reactions have been observed; therefore, the drug should be discontinued at the first sign of sensitization. While these symptoms will usually disappear spontaneously, symptomatic treatment may be indicated in some cases.

DOSAGE AND ADMINISTRATION

(See WARNINGS and PRECAUTIONS.)

Dosage should be adjusted according to the indication for therapy, severity of symptoms and the response of the patient.

CAPSULES, 300 mg

Usual Adult Dosage

One 300 mg capsule t.i.d. or q.i.d.

SUPPOSITORIES, 200 mg (not to be used in premature or newborn infants)

Usual Adult Dosage

One suppository (200 mg) t.i.d. or q.i.d.

Usual Children's Dosage

Under 30 lbs: One-half suppository (100 mg) t.i.d. or q.i.d.

30 to 90 lbs: One-half to one suppository (100 to 200 mg) t.i.d. or q.i.d.

SUPPOSITORIES, PEDIATRIC, 100 mg (not to be used in premature or newborn infants)

Usual Children's Dosage

Under 30 lbs: One suppository (100 mg) t.i.d. or q.i.d.

30 to 90 lbs: One to two suppositories (100 to 200 mg) t.i.d. or q.i.d.

INJECTABLE, 100 mg/mL (not for use in children)

Usual Adult Dosage

2 mL (200 mg) t.i.d. or q.i.d. intramuscularly.

NOTE: The injectable form is intended for intramuscular administration only; it is not recommended for intravenous use.

Intramuscular administration may cause pain, stinging, burning, redness and swelling at the site of injection. Such effects may be minimized by deep injection into the upper outer quadrant of the gluteal region, and by avoiding the escape of solution along the route.

Rx Only

STORAGE

Store at 25°C (77°F).

Excursions permitted to 15–30°C (59–86°F).

[See USP Controlled Room Temperature]

HOW SUPPLIED

Capsules, 300 mg trimethobenzamide hydrochloride each, bottles of 100 and 500

NDC 61570-079-01 300 mg 100's

NDC 61570-079-05 300 mg 500's

Suppositories, Pediatric, 100 mg, boxes of 10

Suppositories, 200 mg, boxes of 10 and 50

NDC 61570-503-10 100 mg (box of 10)

NDC 61570-504-10 200 mg (box of 10)

NDC 61570-504-50 200 mg (box of 50)

Ampuls, 2 mL, boxes of 10

NDC 61570-540-02 100 mg/mL in 2 mL ampul

Multi-Dose Vials, 20 mL

NDC 61570-541-20 100 mg/mL in 20 mL Multi-Dose Vials

NDA 17-531/S-010
Distributed By: Monarch Pharmaceuticals, Inc., Bristol, TN 37620

Manufactured By: King Pharmaceuticals, Inc., Bristol, TN 37620

Rev. 5/01

0934128

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/s/

Robert Temple
12/13/01 06:36:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

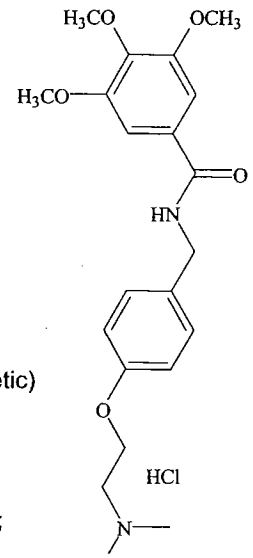
APPLICATION NUMBER: 17-531/S-010

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA NUMBER: **17-531**
4. SUPPLEMENT NUMBERS/DATES: SE2-010
   letterdate: 08-FEB-01
   stampdate: 14-FEB-01
5. AMMENDMENTS/REPORTS/DATES: 09-MAR-01
   02-APR-01
6. RECEIVED BY CHEMIST: 16-FEB-01

7. APPLICANT NAME AND ADDRESS: King Pharmaceuticals
   501 Fifth Street
   Bristol, TN 37620



8. NAME OF DRUG: Tigan Capsules
9. NONPROPRIETARY NAME: trimethobenzamide hydrochloride
10. CHEMICAL NAME/STRUCTURE:

N-[*p*-[2-(dimethylamino)ethoxy]benzyl]-3,4,5-trimethoxybenzamide monohydrochloride
CAS registry # [554-92-7]

11. DOSAGE FORM(S): Capsules
12. POTENCY: 300 mg
13. PHARMACOLOGICAL CATAGORY: control of nausea and vomiting (anti-emetic)
14. HOW DISPENSED: XXX (RX) ____ (OTC)
15. RECORDS & REPORTS CURRENT: XXX (YES) ____ (NO)

16. RELATED IND/NDA/DMF: NDA 11-853 (Roche, Tigan Injection);
    NDA 11-854 (Roche, Tigan Capsules) NDA 17-529 (King, Tigan Suppositories);
    NDA 17-530 (King, Tigan Injection)
    Supporting Documents

17. **SUPPLEMENT PROVIDES FOR:** a 300-mg formulation of Tigan Capsules.

18. COMMENTS: Tigan is a DESI drug. This submission is provided to resolve a directive of a Jan. 1979 Federal Register Notice whereby it was ordered that Tigan Capsules be reformulated. By agreement with DNPDP, Tigan capsules of the 100 mg and 250 mg strengths will be discontinued and replaced by a 300 mg formulation. The specifications and regulatory methods follow those of the USP monograph for trimethobenzamide hydrochloride capsules. The Biopharmaceutics reviewer finds the dissolution method and specifications adequate. Nine months of stability data were presented for the new 300-mg capsule formulation. This reviewer concurs with the assignment of a 2-year expiration date, based on the data of the current submissions and previous supporting data (AR) from the prior 250-mg formulation. Changes to the draft labeling are recommended. Methods validation by Agency laboratories is recommended for the HPLC stability indicating method. The EER report recommends the manufacturing facility as acceptable.

19. CONCLUSIONS AND RECOMENDATIONS: Recommend NDA 17-531 / SE-010 as APPROVABLE. Additional information should be requested. See last page for details of recommendations for labeling revision, an information request and a suggestion.

20. REVIEWER NAME SIGNATURE DATE COMPLETED

Thomas A. Broadbent, Ph.D. _____ 29-MAY-01

cc: Orig. NDA 17-531
HFD-120/DivFile
HFD-120/MShin
HFD-120/TBroadbent
HFD-120MGuzewska
INT: MG

filename: N17531.010a.doc

ATTACHMENT C.

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/s/

Thomas Broadbent
6/20/01 03:05:52 PM
CHEMIST

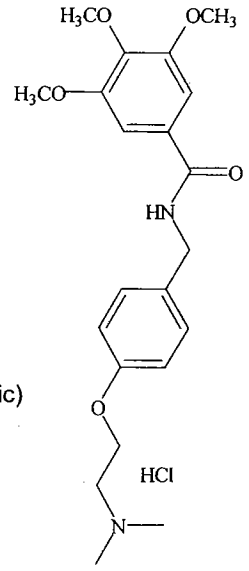
Sentence in comment section revised according to our conversation

Maryla Guzewska
6/20/01 03:11:08 PM
CHEMIST

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA NUMBER: **17-531**
4. SUPPLEMENT NUMBERS/DATES: SE2-010
   letterdate: 08-FEB-01
   stampdate: 14-FEB-01
5. AMMENDMENTS/REPORTS/DATES: 06-JUN-01
   29-JUN-01
6. RECEIVED BY CHEMIST: 14-JUN-01
   03-JUL-01

7. APPLICANT NAME AND ADDRESS: King Pharmaceuticals
   501 Fifth Street
   Bristol, TN 37620



8. NAME OF DRUG: Tigan Capsules
9. NONPROPRIETARY NAME: trimethobenzamide hydrochloride
10. CHEMICAL NAME/STRUCTURE:

N-[*p*-[2-(dimethylamino)ethoxy]benzyl]-3,4,5-trimethoxybenzamide monohydrochloride
CAS registry # [554-92-7]

11. DOSAGE FORM(S): Capsules
12. POTENCY: 300 mg
13. PHARMACOLOGICAL CATAGORY: control of nausea and vomiting (anti-emetic)
14. HOW DISPENSED: XXX (RX) ____ (OTC)
15. RECORDS & REPORTS CURRENT: XXX (YES) ____ (NO)

16. RELATED IND/NDA/DMF: NDA 11-853 (Roche, Tigan Injection);
    NDA 11-854 (Roche, Tigan Capsules) NDA 17-529 (King, Tigan Suppositories);
    NDA 17-530 (King, Tigan Injection)
    Supporting Documents. ———————————————

17. **SUPPLEMENT PROVIDES FOR:** a 300-mg formulation of Tigan Capsules.

18. COMMENTS: This is the second review for this supplement. These two submissions are a response to information requests subsequent to the review of the initial submission and two amendments. These amendments (the third and fourth amendments) also present new provisions. These amendment ———————————
    for the proposed 300 mg Tigan Capsule commercial product and larger bottle sizes. These submissions also propose a new packaging configuration, a physician sample (4-capsule 30 cc HDPE bottle with CRC). New studies have been initiated to monitor the stability of the proposed commercial product and the new sample configuration. Responses to the IR items are summarized starting on the next page. Standard review notes follow.

19. CONCLUSIONS AND RECOMENDATIONS: Recommend APPROVAL of NDA 17-531 / SE-010 with recommendations for labeling (see attachment on last page). A consult from OPDRA for labeling of the 100 & 500 count bottles is pending. PK review is pending. Labeling remains under review; all other CMC provisions appear adequate. The recommended expiration dating for the new products is for ————

20. REVIEWER NAME SIGNATURE DATE COMPLETED

Thomas A. Broadbent, Ph.D. _____ 25-JUL-01

cc: Orig. NDA 17-531
HFD-120/DivFile
HFD-120/MShin
HFD-120/TBroadbent
HFD-120MGuzewska
INT: MG

filename: N17531.010b.doc

ATTACHMENT D

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/s/

Thomas Broadbent
7/25/01 04:09:02 PM
CHEMIST

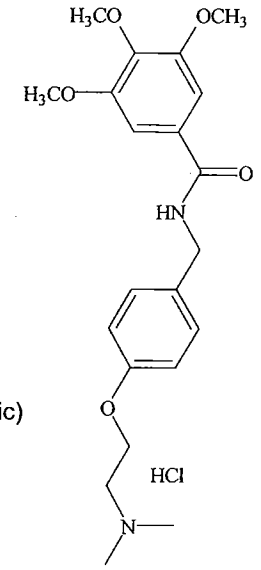
revised recommendations according to conversation

Maryla Guzewska
7/25/01 04:14:48 PM
CHEMIST

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA NUMBER: **17-531**
4. SUPPLEMENT NUMBERS/DATES: SE2-010
   letterdate: 08-FEB-01
   stampdate: 14-FEB-01
5. AMMENDMENTS/REPORTS/DATES:
   letterdate: 10-OCT-01
   stampdate: 11-OCT-01
6. RECEIVED BY CHEMIST: 11-OCT-01

7. APPLICANT NAME AND ADDRESS: King Pharmaceuticals
   501 Fifth Street
   Bristol, TN 37620



8. NAME OF DRUG: Tigan Capsules
9. NONPROPRIETARY NAME: trimethobenzamide hydrochloride
10. CHEMICAL NAME/STRUCTURE:

N-[*p*-[2-(dimethylamino)ethoxy]benzyl]-3,4,5-trimethoxybenzamide monohydrochloride
CAS registry # [554-92-7]

11. DOSAGE FORM(S): Capsules
12. POTENCY: 300 mg
13. PHARMACOLOGICAL CATAGORY: control of nausea and vomiting (anti-emetic)
14. HOW DISPENSED: XXX (RX) ____ (OTC)
15. RECORDS & REPORTS CURRENT: XXX (YES) ____ (NO)
    SPECIAL PRODUCTS _____ Yes XXX No

16. RELATED IND/NDA/DMF: NDA 11-853 (Roche, Tigan Injection);
    NDA 11-854 (Roche, Tigan Capsules) NDA 17-529 (King, Tigan Suppositories);
    NDA 17-530 (King, Tigan Injection)
    Supporting Documents ———————————————

17. **SUPPLEMENT PROVIDES FOR:** a 300-mg formulation of Tigan Capsules.

18. COMMENTS: This is the third CMC review for this supplement. This submission provides updated stability data for proposed commercial configurations of Tigan Capsules, 300 mg. It also contains commitments to comply with three recommendations for labeling. The biopharmaceutics review has recommended approval. An OPDRA consult has been forwarded to DNPDP with labeling recommendations. The EER recommendation of acceptable is current.

19. CONCLUSIONS AND RECOMENDATIONS: Recommend APPROVAL of NDA 17-531 / SE2-010.
    The recommended expiration dating for the new products is for 24 months.

20. REVIEWER NAME SIGNATURE DATE COMPLETED

Thomas A. Broadbent, Ph.D. _____ 12-OCT-01

cc: Orig. NDA 17-531
HFD-120/DivFile
HFD-120/MShin
HFD-120/TBroadbent
HFD-120MGuzewska
INT: MG

filename: N17531.010c.doc

ATTACHMENT A

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/s/

Thomas Broadbent
11/1/01 09:42:59 AM
CHEMIST

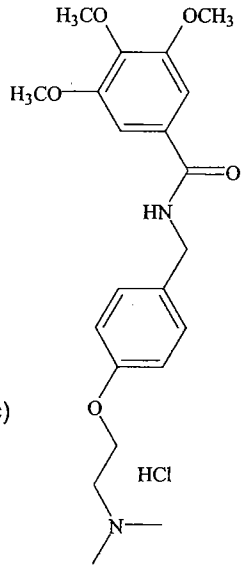
initialled 10/31/01

Maryla Guzewska
11/1/01 10:20:34 AM
CHEMIST

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA NUMBER: **17-531**
4. SUPPLEMENT NUMBERS/DATES: SE2-010
   letterdate: 08-FEB-01
   stampdate: 14-FEB-01
5. AMMENDMENTS/REPORTS/DATES: e-mail & Telephone
6. RECEIVED BY CHEMIST: 21-NOV-01

7. APPLICANT NAME AND ADDRESS: King Pharmaceuticals
   501 Fifth Street
   Bristol, TN 37620



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9. NONPROPRIETARY NAME: trimethobenzamide hydrochloride
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N-[*p*-[2-(dimethylamino)ethoxy]benzyl]-3,4,5-trimethoxybenzamide monohydrochloride
CAS registry # [554-92-7]

11. DOSAGE FORM(S): Capsules
12. POTENCY: 300 mg
13. PHARMACOLOGICAL CATAGORY: control of nausea and vomiting (anti-emetic)
14. HOW DISPENSED: XXX (RX) ____ (OTC)
15. RECORDS & REPORTS CURRENT: XXX (YES) ____ (NO)
    SPECIAL PRODUCTS ____ Yes XXX No

16. RELATED IND/NDA/DMF: NDA 11-853 (Roche, Tigan Injection);
    NDA 11-854 (Roche, Tigan Capsules) NDA 17-529 (King, Tigan Suppositories);
    NDA 17-530 (King, Tigan Injection)
    Supporting Documents: ———————————————

17. **AMENDED SUPPLEMENT PROVIDES FOR:** the final drafts of the 100-count bottle label and the package insert of 300 mg Tigan Capsules.

18. COMMENTS: This is the fourth CMC review for this supplement. This contains the final drafts of the package insert (CMC portion) and the bottle label for the 100-count presentation that were negotiated by the project manager and the sponsor through e-mail and telephone conversation. All CMC recommendations for the package insert have been incorporated. The bottle label is acceptable to the CMC review team. OPDRA has indicated that the bottle label is acceptable.

19. CONCLUSIONS AND RECOMENDATIONS: Recommend APPROVAL of NDA 17-531 / SE2-010.
    The recommended expiration dating for the new products is for 24 months.

20. REVIEWER NAME SIGNATURE DATE COMPLETED

Thomas A. Broadbent, Ph.D. _____ 28-NOV-01

cc: Orig. NDA 17-531
HFD-120/DivFile
HFD-120/MShin
HFD-120/TBroadbent
HFD-120MGuzewska
INT: MG

filename: N17531.010d.doc

ATTACHMENT 13

3 page(s) of draft labeling has been removed from this portion of the review.

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/s/

Thomas Broadbent
11/28/01 11:50:12 AM
CHEMIST

initialled 11/28/01

Maryla Guzewska
11/28/01 03:11:30 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-531/S-010

CLINICAL PHARMACOLOGY BIOPHARMACEUTICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Date: 2/8/01, 2/23/01, 3/9/01

NDA:	17-531
Name of Drug:	Tigan (Trimethobenzamide HCL) Capsules
Indication of Drug:	Anti-emetic Agent
Sponsor:	King Pharm., Bristol, Tennessee
Type of Submission:	Fulfillment of DESI Notice
Reviewer:	Hong Zhao, Ph.D.

Introduction

Tigan (trimethobenzamide HCl) is indicated for the treatment of nausea and vomiting. Tigan is currently available as 100 mg and 250 mg capsules and 100 mg/ml solution for intramuscular (IM) injection. To bring Tigan capsules into compliance with the Federal Register Notice of January 9, 1979, the sponsor has reformulated the Tigan Capsules to 300 mg and 400 mg capsules to determine which one is the optimal dose to achieve plasma levels that are comparable to those following IM injection of 2 ml of 100 mg/ml trimethobenzamide at which dose clinical efficacy has been demonstrated. This Amendment to pending Application NDA17-531 is to provide for the approval of a 300-mg formulation of Tigan Capsules.

Bioavailability Study Review

Rationale for the Study

This study is being performed to choose the oral dose of Tigan capsule (300 mg or 400 mg) that will result in a comparable pharmacokinetic profile to that of an IM injection of 2 ml of 100 mg/ml (200 mg dose) trimethobenzamide solution.

Study Design

This is a single-dose, four-way crossover study to assess the bioavailability of three oral Tigan formulations compared to Tigan IM injectable. The formulations to be studied include the currently marketed 100 mg capsule, 100 mg/ml IM injectable formulation, and the new 300 mg and 400 mg capsules. Seventy-four healthy, non-smoking male and female volunteers (18-65 years old) in two consecutive cohorts took a single dose of each medication under fasting condition with a minimum of 5-day washout period between each regimen. Four treatments are listed in the table below:

Treatment	100mg (current)	300mg (new)	400mg (new)	100mg/ml (I.M.)
Dose	4x100mg	1x300mg	1x400mg	200mg (2 mL)
Lot # (Exp.)	KW02 (12/03)	C002 (2/02)	C003 (2/02)	NA14 (01/05)
Blood Sampling: 0, 0.083, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours post-dose.				

Trial Medications

The 100 mg capsules and the injectable formulation used in the study are the currently marketed formulations. The 300 mg and 400 mg capsules were manufactured and provided by the sponsor. The 300 mg and 400 mg capsules are the same formulation as the 250 mg capsules that are currently marketed by the sponsor. The only difference between the currently marketed 250 mg capsules, and the 300 mg and 400 mg capsules

used in this study was the fill weight. The amounts of each ingredient, active and excipients, are listed below:

Capsule	Trimethobenzamide HCL USP*	Lactose NF	Starch NF	Magnesium Stearate NF	Fill Weight
100 mg					
250 mg					
300 mg					
400 mg					

* = all comp
† = amount i

Bioanalytical Analysis

Blood samples obtained during the study were analyzed using a validated LC-MS assay. The validation results are shown below:

	Quality Sample	LOQ	Linearity	IS

This LC/MS method for the determination of trimethobenzamide in human plasma was shown to be reproducible, specific, and sufficiently sensitive, linear, precise, and accurate. No significant degradation was observed for trimethobenzamide in human plasma under different storage conditions. The results of human plasma concentrations of trimethobenzamide in this study are acceptable.

PK Results

Sixty-eight (68) out of seventy-four (74) subjects completed the study (59 from Cohort 1, 9 from Cohort 2). The study results are shown in the following tables and the c-t plot is shown in the Appendix.

Parameter Treatment	C_{max}* (ng/ml)	AUC_{0-t}* (ng.h/ml)	$AUC_{0-\infty}$* (ng.h/ml)	T_{max}** (h)	$t_{1/2}$** (h)	F**
200 mg IM	3729 (27%)*	10124 (17%)	10465 (17%)	0.54±0.21	6.8±1.7	
300mg Capsule	3817 (36%)	9461 (26%)	10218 (26%)	0.78±0.24	7.8±2.4	0.65±0.09
400mg Cap.	5211 (34%)	12668 (27%)	13647 (28%)	0.73±0.22	7.4±2.0	0.65±0.11
4x100mg Cap.	5198 (30%)	12426 (27%)	13493 (27%)	0.66±0.20	8.0±2.3	0.64±0.11

*Mean (CV%), **Mean±SD.

Test vs. Reference (200mg IM) Geometric Least Squares Means Ratio (90% CI)			
	300mg Capsule	400mg Capsule	4x100mg Capsule
C_{max}	**100.0 (93.9-106.5)**	136.0 (127.7-144.9)	138.0 (129.5-146.9)
AUC_{0-t}	**91.9 (89.5-94.5)**	122.2 (118.9-125.6)	120.1 (116.8-123.4)
$AUC_{0-\infty}$	**96.0 (93.3-98.7)**	127.5 (124.0-131.2)	126.0 (122.5-129.6)

Summary

- The C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for the 300 mg capsule were comparable to those for the 200 mg IM injection (geometric least squares mean ratios and 90% confidence intervals all fell within the 80%-125% confidence limit).
- The T_{max} for oral capsules differed from the IM injection by 15 minutes.

Safety

Six (6) subjects prematurely withdrew from the study. Four of six were due to adverse events: conjunctivitis (1), rash (1), vomiting (1) and leg cramp (1). The other two were due to noncompliance or difficult blood draws. Trimethobenzamide hydrochloride appeared to be safe and well tolerated with no significant differences in safety among the 4 treatment periods. Twenty-one (21) adverse events were determined to be related to study treatment; all were of mild to moderate intensity with neurologic complaints being the most frequent. Neurologic-related adverse events are well-known side effects of trimethobenzamide hydrochloride. No unexpected adverse events were observed.

Subpopulation PK Analyses

Effect of Gender on Trimethobenzamide PK

	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng.h/ml)	$t_{1/2}$ (h)
IM 200 mg (Male, N=40)	3537±948	10581±2405	7.0±1.9
(female, N=28)	4002±1019	10621±1583	6.7±1.4
Capsule 300 mg (male, N=40)	3536±1105	10041±2729	7.8±2.3
(female, N=28)	4219±1583	10436±2683	7.8±2.5

Effect of Race on Trimethobenzamide PK

	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng.h/ml)	$t_{1/2}$ (h)
IM 200 mg (White, N=53)	3712±994	10448±1923	6.8±1.7
(Black, N=12)	3982±1038	11544±2779	6.5±1.6
Capsule 300 mg (White, N=53)	3847±1304	10371±2796	8.0±2.3
(Black, N=12)	3863±1712	9768±2465	7.6±2.7

Summary

- It appears that neither gender nor race has any effect on trimethobenzamide pharmacokinetics.

Previous BE Study (17-531-O.S.2, 1979)

Study Design

This was a 3-way crossover study to assess the bioavailability of two oral Tigan formulations (250 mg capsule and 400 mg oral solution) compared to Tigan IM Injectable (2 ml of 100 mg/ml). A total of 24 healthy male and female volunteers completed this study. Washout period between treatments was one week. Serum samples for determination of trimethobenzamide concentrations were collected at the following

time points: 0 (pre-dose) and 20, 40 min, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours post each drug treatment.

PK Results

Parameter Treatment	C_{max}* (ng/ml)	AUC_{0-t}* (ng.h/ml)	$AUC_{0-\infty}$* (ng.h/ml)	T_{max}** (h)	$t_{1/2}$** (h)	F**
200 mg IM	4238 (28%)	11128 (26%)	12116 (34%)	0.67±0.36	4.5±2.4	
250mg Capsule	4307 (36%)	9269 (57%)	11584 (62%)	0.81±0.72	4.8±1.8	0.70±0.14
400mg Solution	6812 (48%)	13971 (61%)	17014 (64%)	0.61±0.28	4.4±1.3	0.65±0.14

*Mean (CV%), **Mean±SD

Geometric Least Squares Means Ratio (90% CI)		
	250mg Capsule/200 mg IM	400mg Solution/200mg IM
C_{max}	97.8 (86.2-110.9%)	153.5 (135.3-174.2%)
AUC_{0-t}	78.1 (72.6-83.9%)	115.4 (107.4-124.0%)
$AUC_{0-\infty}$	84.0 (76.7-92.0%)	125.0 (114.7-136.1%)

Summary

- The systemic exposures of the 250 mg capsule and the 400 mg oral solution are not comparable to that of the 200 mg IM injection.
- Based on the relative bioavailability of the 250 mg capsule to the 200 mg IM injection, the dose expected to achieve similar trimethobenzamide concentrations for the capsule would be approximately 300 mg.
- Based on the relative bioavailability of the 400 mg solution to the 200 mg IM injection, the dose expected to achieve similar trimethobenzamide concentrations for solution would be approximately 320 mg.
- The pharmacokinetics of trimethobenzamide following an oral 250 mg capsule or an oral 400 mg solution exhibit a moderate to high degree of variability and the 200 mg IM injection is less variable.

Dissolution Test

The sponsor provided dissolution data (see table below) using the current dissolution method as shown below:

Apparatus: USP Apparatus I (baskets) rotated at 100 rpm

Dissolution medium: 900 mL of water at 37±0.5°C

Specification: [redacted]

Dissolution Data from Tigan 300 mg Capsules (Lot C002, Biobatch)

Time (min)	[redacted]
% Dissolved±SD	
Range	

Summary

- The dissolution data on the 300 mg capsule biobatch (Lot C002) showed that each individual capsule had ove[redacted]

Comment 1
The pharmacokinetic results indicate that the 300 mg capsule is comparable to the 200 mg IM injection. These results address the issues in the January 9, 1979 Federal Register with respect to trimethobenzamide capsules and therefore the 300 mg capsule formulation can be used to replace the 250 mg capsule that are currently marketed.

Comment 2
The dissolution data on the biobatch showed that each individual capsule had over — of the drug dissolved in ——— Therefore, the recommended dissolution specification for Tigan 300 mg capsule should be ———————

Comment 3
Since no pharmacokinetic information is included in the Tigan product labeling, this NDA review gives an opportunity to generate such information for general PK description in the labeling for both Tigan IM and oral capsule products. Therefore, comparison of PK parameters between different populations (men vs. women, Caucasians vs. Blacks) were conducted. However, information regarding the metabolic fate of trimethobenzamide is lacking. The sponsor is requested to provide this information for labeling purposes.

OCPB Suggested Statements for Pharmacokinetic Section of the Labeling:
CLINICAL PHARMACOLOGY
Pharmacokinetics
The pharmacokinetics of trimethobenzamide have been studied in healthy adult subjects. Following administration of 200 mg (100 mg/ml) Tigan I.M. injection, the time to reach maximum plasma concentration (T_{max}) ——————— A single dose of Tigan 300 mg capsul ——————— The relative bioavailability of capsule formulation compared to the solution is 100%. The mean elimination half-life of trimethobenzamide is 7 to 9 hours.

Special Population
Gender
Systemic exposure to trimethobenzamid — similar between men (N=40) and women (N=28).

Race
———————
(N=53) and African Americans (N=12).

Recommendation
This submission (NDA17-531) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and has been found to be acceptable for meeting the OCPB requirements.

The systemic exposure of the 300 mg capsule has been shown comparable to that of the 200 mg IM injection which addressed the issues in the January 9, 1979 Federal Register

with respect to trimethobenzamide capsules. Therefore the 300 mg capsule formulation can be used to replace the 250 mg capsules that are currently marketed.

The sponsor is requested to adopt the OCPB suggested labeling as provided in Comment #3. In addition, the sponsor is requested to provide information regarding the metabolic fate of trimethobenzamide for labeling purposes.

Also, the sponsor is requested to adopt the following dissolution method and specification for Tigan 300 mg Capsules:

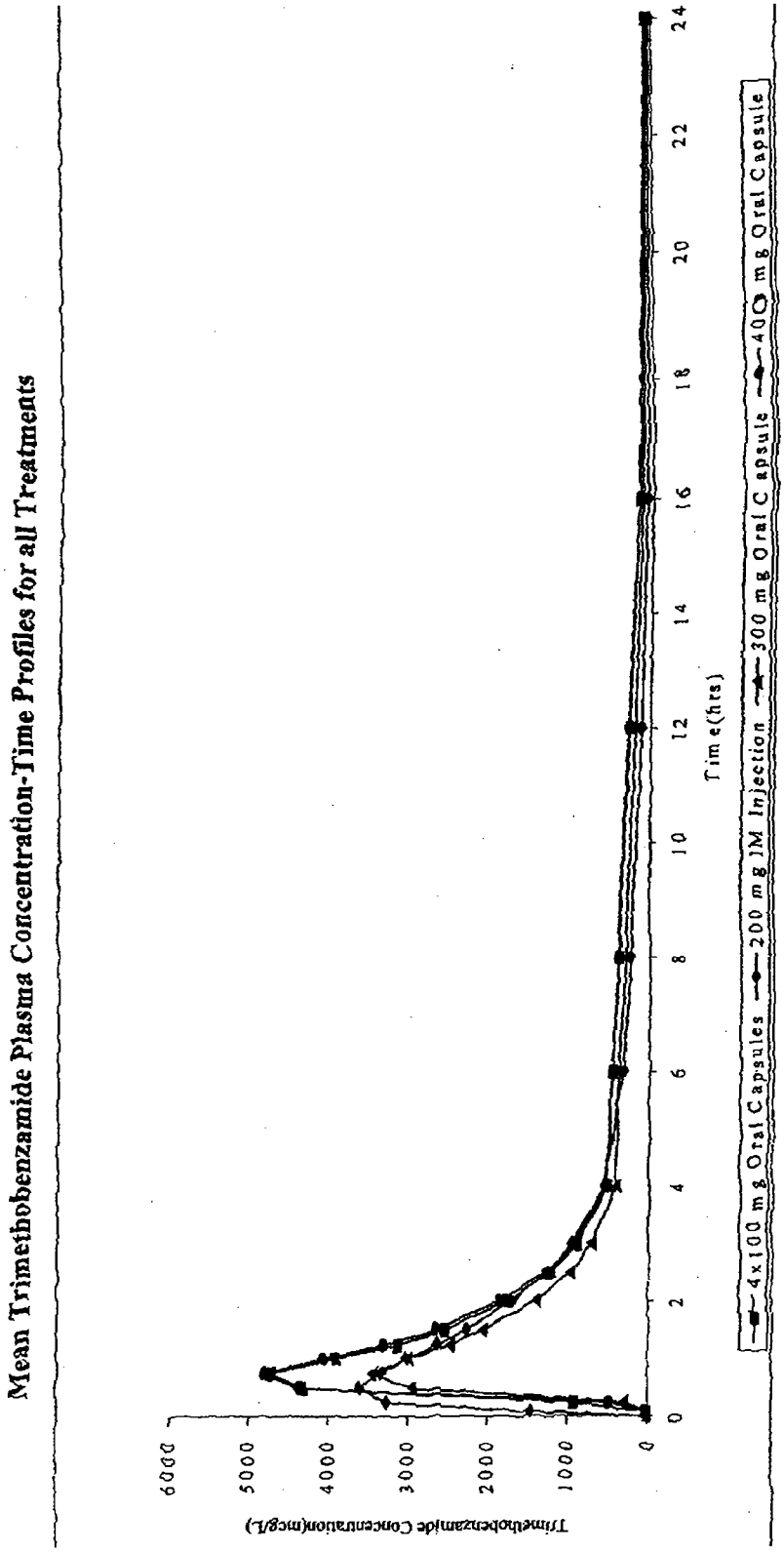
Apparatus:	USP Apparatus I (baskets) rotated at 100 rpm
Dissolution medium:	900 mL of water at 37±0.5°C
Proposed specification:	NLT [redacted] (Q) is dissolved in 30 minutes

Hong Zhao, Ph.D. _____

RD/FT Initialed by Raman Baweja, Ph.D. _____

cc: NDA 17-531 (Tigan Capsules) HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

Appendix


Mean Trimethobenzamide Plasma Concentration-Time Profiles for all Treatments
Trimethobenzamide Concentration(mcg/L)
6000
5000
4000
3000
2000
1000
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time(hrs)
4x100 mg Oral Capsules
200 mg IM Injection
300 mg Oral Capsule
400 mg Oral Capsule

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/s/

Hong Zhao
9/28/01 03:46:49 PM
BIOPHARMACEUTICS

Raman Baweja
9/28/01 04:11:25 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-531/S-010

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 17-531 SUPPL # 10

Trade Name Tigan 300mg Capsules

Generic Name Trimethobenzamide Hydrochride

Applicant Name King Pharmaceuticals HFD- 120

Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE2

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /_X_/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /_X_/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Melaine Shin, R.Ph
Signature of Preparer
Title: Regulatory Management Officer

November 8, 2001
Date

Russell Katz, M.D.
Signature of Office or Division Director

Date

cc:
Archival NDA
HFD-120/Division File
HFD-120/Shin
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Russell Katz
12/18/01 08:49:54 AM

REGULATORY PROJECT MANAGER
LABELING REVIEW

DRUG: Tigan Capsules (NDA 17-531)

SPONSOR: King Pharmaceuticals.

Supplements:
(last approved) NDA 17-531 SE2-010 (approval date 12/13/01) with the draft labeling.

(pending action)

NDA 17-531
SE2-010/FPL (1/18/02)

REVIEW

17-531/SE2-010 **Approved Draft Labeling dated 12/13/01**
17-531/SE2-010 **FPL submitted 1/18/02** **Label Code:** **PI:** **0934128**

CONCLUSIONS

- The FPL (NDA 17-531) dated 1/18/02 was compared to the approved draft labeling from the approval of NDA 17-531 dated 12/13/01, and it was identical to the approved draft labeling.
- I recommend acknowledge and accept the FPL (NDA 17-531) and superced

Melaine Shin, R.Ph.
Regulatory Management Officer

Robbin Nighswander, R.Ph.
Superrvisory Regulatory Health Project Manager

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/s/

Melaine Shin
3/21/02 03:14:40 PM
CSO

Robbin Nighswander
3/26/02 06:00:13 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-531 / S-010

INFORMATION REQUEST LETTER

King Pharmaceuticals, Inc.
Attention: Dean Cirotta
Senior Director, Regulatory Affairs
501 Fifth Street
Bristol, Tennessee 37620

Dear Mr. Cirotta:

Please refer to your February 8, 2001 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tigan (trimethobenzamide hydrochloride) Tablets 300 mg.

We also refer to your submissions dated March 9, 2001 and April 2, 2001.

We are reviewing the Chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental NDA.

1. Please provide the acceptance specifications for th[redacted] of the new Tigan 300 mg capsule formula, including any that may relate to QA regarding BSE (bovine spongiform encephalopathy).

2. Please provide a current letter of authorization for the DMF for the [redacted]

3. Please provide a description of the sampling procedures for release testing for Tigan 300 mg capsules.

4. Please confirm that the container/closure system for the 300 mg capsules is the same as that provided for the previously marketed 100 mg and 250 mg capsules.

5. Please provide additional stability data for the 300 mg capsules, if updated information is available.

6. We note that the capsule counts (100 and 500) for the bottle configurations in the draft labeling do not reflect the configurations described in the submission text and batch records [redacted] Please clarify.

If you have any questions, call Melaine Shin, Regulatory Health Project Manager, at 301-594-2850.

Sincerely,

Maryla Guzewska, Ph.D.
Chemistry Team Leader, Neurology Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC 1, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Maryla Guzewska
5/30/01 04:23:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-529/S-009
NDA 17-530/S-018
NDA 17-531/S-010

King Pharmaceuticals, Inc.
Attention: Dean R. Cirotta, MBA
Senior Director, Regulatory Affairs
501 Fifth Street
Bristol, TN 37620

Dear Mr. Cirotta:

Please refer to your new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tigan (trimethobenzamide hydrochloride) 100 and 200 mg suppositories (NDA 17-529), 200 mg/2 ml injection (NDA 17-530), and 300 mg capsules (NDA 17-531).

Reference is also made to an Agency letter dated December 13, 2001, providing for the approval of supplemental application 17-531/S-010.

We additionally refer to your labeling supplements, NDAs 17-529/S-009 & 17-531/S-018, dated December 19, 2001, submitted under "Changes Being Effected", providing for revisions to the labeling in accordance with the Agency letter dated December 13, 2001.

We have completed the review of these supplemental applications, NDAs 17-529/S-009 & 17-531/S-018, 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 submitted final printed labeling (package insert submitted December 19, 2001/Label Code 0934128). Accordingly, these supplemental applications are approved effective on the date of this letter.

Additionally, we acknowledge receipt of your submission to NDA 17-531/S-010 dated January 18, 2002, providing for 20 copies of FPL as requested in our approval letter dated December 13, 2001.

We have completed our review of the labeling (Label Code 0934128) submitted on January 18, 2002, and it is acceptable. Therefore, this labeling will be retained in our files.

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, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
4/30/02 08:04:27 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-531/S-010

PRIOR APPROVAL SUPPLEMENT

King Pharmaceuticals, Inc
Attention: Dean R. Cirotta, MBA
Senior Director, Regulatory Affairs
501 Fifth Street
Bristol, Tennessee, 37620

Dear Mr. Cirotta:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tigan (trimethobenzamide hydrochloride) Capsules

NDA Number: 17-531

Supplement Number: S-010

Review Priority Classification: Standard (S)

Date of Supplement: February 8, 2001

Date of Receipt: Februay 14, 2001

This supplement proposes the approval of a 300-mg formulation of Tigan (trimethobenzamide hydrochloride) Capsules.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 15, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 14, 2001 and the secondary user fee goal date will be February 14, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of

21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Melaine Shin, R.Ph., Regulatory Management Officer, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Melaine Shin
3/1/01 09:20:36 AM
Signed for John S. Purvis

MEMORANDUM OF MEETING MINUTES

Meeting Date:	March 30, 2001
Time:	11:00AM
Location:	Woodmont II, Conference Room E
Application:	**NDA 17-531 Tigan Capsules**
Meeting Recorder:	Melaine Shin, R.Ph.

FDA Attendees:

Russell Katz, M.D., Division Director
Armando Oliva, M.D., Clinical Team Leader
Leonard Kapcala, M.D., Medical Officer
Mona Zarifa, Ph.D., CMC
Thomas Broadbent, CMC Reviewer
David Read, Acting Director, Regulatory Policy Staff
Brian Pendleton, Regulatory Counsel
Melaine Shin, R.Ph., Regulatory Management Officer

Background: **This efficacy supplement provides for the approval of a 300mg capsule in order to comply with the 1979 federal register notices.**

Discussion Points:

- There is no need for the pediatric studies, and the PM will inform the sponsor accordingly.
- All review teams involved agreed that this supplement is filable.
- This application is due on December 14, 2001.

Post-meeting note:

- All reviews will be ready for the Clinical Team Leader by August 14, 2001.

Action Items:

- Prepare MM and circulate to all disciplines.
- Inform the sponsor that no pediatric studies are required.

Minutes Preparer:_____
Melaine Shin, R.Ph.
Regulatory Management Officer

/s/

Armando Oliva
4/5/01 08:26:57 AM

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA#	NDA 17-531 / SE2-10
DATE:	28 June 2001
PRODUCT NAME:	Tigan Capsules
COMPANY NAME:	King Pharmaceuticals
SUBJECT:	Label for physician sample and updated product stability
CONVERSATION WITH:	Dean Cirotta, Senior Director, Regulatory Affairs
TELEPHONE #:	(423) 274-8663

I called Mr. Cirrotta 6/28/01 10:43 AM to request two items concerning Tigan Capsules, NDA 17-531 / SE2-10). I requested stability updates for the proposed commercial product configurations, as updates become available. (The commercial products are 300 mg Tigan capsules, 4 in a 30 cc bottle (physician sample), 100 in a 120 cc bottle & 500 in a 625 cc bottle.)

I also requested the bottle label for the new 4-count physician sample. I said that simple printed images of the label would be adequate. I noted that I was not able to open the label images in EPS (encapsulated PostScript) files included on a disk sent in the 3/9/01 submission, but that images in electronic format are only optional.

Mr. Cirrotta said that he would send 2 copies of the label for the physician sample. He said that a 2-month stability update for the proposed configurations may already be available and that it would be submitted if it is available.

Thomas A. Broadbent, Ph.D.
Review Chemist
Neuropharmacological Drug Products

cc: HFD-120/NDA 17-531
HFD-120/DivFile
HFD-120/MGuzewska
HFD-120/TBroadbent
HFD-120/MShin

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/s/

Thomas Broadbent
6/29/01 01:46:38 PM
CHEMIST

initialled 6/29/01

Maryla Guzewska
6/29/01 02:59:14 PM
CHEMIST

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA#	NDA 17-531 / SE2-10
DATE:	11 October 2001
PRODUCT NAME:	Tigan Capsules
COMPANY NAME:	King Pharmaceuticals
SUBJECT:	Labeling recommendations and stability update
CONVERSATION WITH:	Dean Cirotta, Senior Director, Regulatory Affairs
TELEPHONE #:	(423) 274-8663

Mr. Cirotta called me (10/10/01) to notify me that the amendment containing updated stability data and labeling commitments for Tigan Capsules, 300 mg was being faxed to me. I returned his call and a fax to clarify the current Uniform Storage Statement that had been described earlier in our October 9 conversation.

The text of the fax:

Uniform Storage Statement (USS)

Full form:

Store at 25°C (77°F)
Excursions permitted to 15-30°C (59° to 86°F)
[See USP Controlled Room Temperature]

Abbreviated forms:

Store at 25°C (77°F)
Excursions 15-30°C (59-86°F)

OR

Store at 25°C (77°F) (see insert)

These are the currently accepted forms of the USS. See the Agency's draft guidance, "*Stability Testing of Drug Substances and Drug Products*," page 19.

Thomas A. Broadbent, Ph.D.
Review Chemist
Neuropharmacological Drug Products, HFD-120

cc: HFD-120/NDA 17-531
HFD-120/DivFile
HFD-120/MGuzewska
HFD-120/TBroadbent
HFD-120/MShin

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/s/

Thomas Broadbent
10/12/01 03:59:49 PM
CHEMIST

initialled 10/12/01

Maryla Guzewska
10/22/01 12:23:49 PM
CHEMIST

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA#	NDA 17-531 / SE2-10
DATE:	09 October 2001
PRODUCT NAME:	Tigan Capsules
COMPANY NAME:	King Pharmaceuticals
SUBJECT:	Labeling recommendations and stability update
CONVERSATION WITH:	Dean Cirotta, Senior Director, Regulatory Affairs
TELEPHONE #:	(423) 274-8663

I called Mr. Cirotta to request a stability update for Tigan Capsules, 300 mg. I also conveyed the three labeling recommendations as given in the 25-JUL-01 CMC review. Mr. Cirotta readily accepted the recommendations. He asked me if our conversation was adequate to convey compliance with the recommendations. I said it was, but he could also include a brief statement with the stability update. Mr. Cirotta said that he would fax the stability update to me, in addition to the formal amendment.

Thomas A. Broadbent, Ph.D.
Review Chemist
Neuropharmacological Drug Products, HFD-120

cc: HFD-120/NDA 17-531
HFD-120/DivFile
HFD-120/MGuzewska
HFD-120/TBroadbent
HFD-120/MShin

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/s/

Thomas Broadbent
10/12/01 11:06:06 AM
CHEMIST

initialled 10/10/01

Maryla Guzewska
10/12/01 02:42:45 PM
CHEMIST

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA# NDA 17-531 / S-010
DATE: May 30, 2001
PRODUCT NAME: Tigan Capsules
COMPANY NAME: King Pharmaceuticals, Inc.
SUBJECT: Information Request
CONVERSATION WITH: Dean Cirotta
TELEPHONE #: (423) 274-8663

I sent Dean Cirotta the text of the May 30 Information Request letter for Tigan Capsules, NDA 17-531 / S-010 by fax ((423) 989-8055). Mr. Cirotta had requested the IR letter to be sent to him by fax in a telephone conference on May 29 with Drs. Guzewska and Broadbent.

Thomas A. Broadbent, Ph.D.
Review Chemist
Neuropharmacological Drug Products

cc: HFD-120/17-531
HFD-120/DivFile
HFD-120/MGuzewska
HFD-120/TBroadbent
HFD-120/MShin

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/s/

Thomas Broadbent
5/31/01 04:59:13 PM
CHEMIST

initialled 5/31/01

Maryla Guzewska
5/31/01 05:36:49 PM
CHEMIST

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA#	NDA 17-531
DATE:	26 March 2001
PRODUCT NAME:	Tigan Capsules
COMPANY NAME:	King Pharmaceuticals
SUBJECT:	SE2-10
CONVERSATION WITH:	Dean Cirotta, Senior Director, Regulatory Affairs
TELEPHONE #:	(423) 274-8663

Dr. Zarifa and Dr. Broadbent contacted Dean Cirotta of King Pharmaceuticals to clarify CMC provisions of SE2-10. We referred to the Agency Guidance, *Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application.*

We requested the following items below. We noted that if the information has been provided in the NDA previously, citation of the location of the information is adequate for our needs.

- A current LOA from the supplier of the drug substance (manufacturer)
- Quantitative capsule composition for the 300 mg capsules (Guidance Section IIB)
- Acceptance specifications for the drug substance (Guidance Section IIC)
- Identification of the product manufacturing facility (Guidance Section IID)

  The facility was confirmed as: King Pharmaceuticals
  501 Fifth Street
  Bristol, Tennessee 37620

- Specifications and methods, including validation, for the drug product (Guidance Section IIF)

  2 copies of method validation packages for analytical methods not previously validated

- Environmental assessment or request for waiver of environmental assessment (Guidance Section IV)

Mr. Cirotta said that he would provide the information in a few days.

Thomas A. Broadbent, Ph.D.
Review Chemist
Neuropharmacological Drug Products

cc: HFD-120/NDA 17-531
HFD-120/DivFile
HFD-120/MGuzewska
HFD-120/TBroadbent
HFD-120/MShin

/s/

Thomas Broadbent
3/27/01 11:43:24 AM
CHEMIST

initialled 3/27/01

Maryla Guzewska
3/27/01 12:55:48 PM
CHEMIST

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA#	NDA 17-531 / SE2-10
DATE:	25 July 2001
PRODUCT NAME:	Tigan Capsules
COMPANY NAME:	King Pharmaceuticals
SUBJECT:	Labeling provisions for identification of lot number and expiration date
CONVERSATION WITH:	Dean Cirotta, Senior Director, Regulatory Affairs
TELEPHONE #:	(423) 274-8663

I called Mr. Cirotta on July 24 to request clarification of the provisions for identification of the lot number and the expiration date on Tigan 100-count and 4-count (physician sample size) bottle labels. Mr. Cirotta did not answer the call, so I left my information request on his voice mail. Mr. Cirotta called back at 8:00 AM the next day, July 25, 2001. He left a voice mail message explaining that there are blank unvarnished areas to the right of the bar codes on the 100-count and 4-count bottle labels. Lot numbers and expiration dates will be imprinted on those areas.

Thomas A. Broadbent, Ph.D.
Review Chemist
Neuropharmacological Drug Products

cc: HFD-120/NDA 17-531
HFD-120/DivFile
HFD-120/MGuzewska
HFD-120/TBroadbent
HFD-120/MShin

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/s/

Thomas Broadbent
7/25/01 04:03:15 PM
CHEMIST

telecon memo, initialled 7/25/01

Maryla Guzewska
7/25/01 04:11:41 PM
CHEMIST

MEMORANDUM OF TELECON

DATE: March 1, 2001

APPLICATION NUMBER: NDA 17-531/S-010, Tigan (trimethobenzamide) Capsules

BETWEEN:

Name: Dean Cirotta, Senior Director, Regulatory Affairs
Phone: 423-274-8663
Representing: King Pharmaceuticals, Tennessee

AND

Name: Melaine Shin, R.Ph., Project Manager
Ray Baweja, Ph.D., OCPB Team Leader
Hong Zhao, Ph.D., OCPB Reviewer
Representing: Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Request for dissolution information and data

King Pharmaceuticals submitted a supplement on February 8, 2001 for Tigan Capsules to comply with the Federal Register Notice of 1979. OCPB review team had requests for additional information from the sponsor.

At the conclusion of the telecon, it was agreed that the following information will be provided as an amendment to the supplement:

- Batch number for each of the four treatments used in Bioequivalence study along with their expiration date.
- Individual capsule dissolution data on 12 units of the 300-mg capsule biobatch and dissolution profiles obtained at 15, 30, 45 and 60 minutes timepoints.
- Mention the dissolution method and medium used to generate the dissolution data.
- Indicate that the stability batch is the same as the biobatch as mentioned by the sponsor during the telecon.

Melaine Shin, R.Ph.
Regulatory Management Officer

/s/

Melaine Shin
3/2/01 09:14:22 AM
CSO

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:	**DUE DATE:**	**OPDRA CONSULT #:**
June 14, 2001	July 31, 2001	01-0133

TO: Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Melaine Shin, Project Manager
HFD-120

PRODUCT NAME:	**MANUFACTURED BY:**
Tigan (Trimethobenzamide Hydrochloride Capsules) 300 mg **NDA #:** 17-531/S-010	King Pharmaceuticals, Inc. **DISTRIBUTED BY:** Monarch Pharmaceuticals, Inc.

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), OPDRA evaluated the proposed container labels and package insert labeling as requested.

OPDRA RECOMMENDATION:
OPDRA recommends the labels and labeling be revised as outlined in section III of this review.

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-32
Center for Drug Evaluation and Research

Labels and Labeling Review

DATE OF REVIEW: **July 23, 2001**

NDA: **17-531/S-010**

NAME OF DRUG: **Tigan (Trimethobenzamide Hydrochloride Capsules) 300 mg**

NDA HOLDER: **Monarch Pharmaceuticals, Inc.**

I. INTRODUCTION

This consult is in response to a June 14, 2001, request from the Division of Neuropharmacological Drug Products (HFD-120), to evaluate the proposed container and package insert labeling. The Division was especially concerned with the prominence of the corporate logo.

PRODUCT INFORMATION
Tigan contains the active ingredient, trimethobenzamide hydrochloride. Trimethobenzamide hydrochloride is indicated for the control of nausea and vomiting. Tigan is currently available in two dosage forms from this manufacturer, suppositories, and injectable. This supplement provides for a new capsule dosage form. Each capsule contains 300 mg of trimethobenzamide hydrochloride. The capsules are supplied in bottles of 100 and 500.

II. RISK ASSESSMENT

The FDA Adverse Event Reporting System *(AERS)* database was searched for all post-marketing safety reports of medication errors reported for the active ingredient term "trimethobenzamide%", trade name "Tigan%", and verbatim for both, using the 1. [redacted], DRUG MALADMINISTRATION to determine if there are any existing problems relating the packaging and labeling of this drug product. This search strategy retrieved six unduplicated medication error reports, none of which was related to the capsule formulation of this product.

The Division requested our comments concerning the sponsors proposed container and insert labeling in particular the prominence (size & color) of the Monarch logo. The draft labels provided for review show the [redacted]

21 CFR 201.10 (g)(2) states "the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features".

Upon completion of our review, we have identified additional labeling deficiencies. See section III of this review for the comments that can be provided to the sponsor.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

OPDRA has reviewed the container labels and package insert labeling and provide the following recommendations for labeling revisions, which might minimize potential user error.

CONTAINER LABEL (100s and 500s)

A.

B.

C.

D. 21 CFR 201.10 (g)(2) states "the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including

typography, layout, contrast, and other printing features". Although the

[redacted]

IV. RECOMMENDATIONS

OPDRA recommends the labeling revisions outlined in section III of this review be implemented upon approval of this supplement.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carol Holquist at (301) 827-0915.

Carol Holquist, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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/s/

Carol Holquist
7/23/01 11:34:32 AM
PHARMACIST

Jerry Phillips
7/25/01 07:58:39 AM
DIRECTOR

Martin Himmel
7/26/01 08:52:16 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: November 8, 2001
From: Armando Oliva, MD
To: Russell Katz, MD
Subject: Tigan Capsules, NDA 17-531 S-010

Tigan (trimethobenzamide HCl) is indicated for the control of nausea and vomiting. The oral capsules are currently available in 100mg and 250mg strengths. In order to bring Tigan capsules in compliance with the Federal Register Notice of 1/9/1979 under DESI, the sponsor has reformulated the capsules to 300mg and 400mg to determine which one is the optimal dose to achieve exposures that are comparable to that achieved following an IM injection of 2ml of the 100mg/ml solution (200mg IM); a parenteral dose which the Agency has determined to have clinical efficacy.

This NDA supplement provides information to support approval of the 300mg capsule as the effective oral dose. I have reviewed the OCPB, chemistry, and OPDRA reviews, and these form the basis for my memorandum.

The supplement relies on the results of a single pharmacokinetic study. Dr. Hong Zhao provides the OCPB review. The PK study was a single-dose, four-way crossover study that compared the following treatments:

- 200mg IM (using the 2 ml of 100mg/mL currently marketed solution)
- 4x100mg capsules PO (using the currently marketed capsule)
- 300mg capsule PO
- 400mg capsule PO

The sponsor provided the 300mg and 400mg capsules in this study. The only difference between these and the currently marketed 250mg capsule is the fill weight.

Seventy-four (74) healthy, non-smoking males and females, aged 18-65, took a single dose of Tigan under fasting conditions with a minimum 5-day washout period between each regimen. Blood sampling occurred at appropriate time intervals for 24 hours.

Sixty-eight (68) of the 74 subjects completed the study. The results are shown in Table 1 (OCPB review table, page 2).

Table 1: Tigan PK Results

Parameter Treatment	C_{max}* (ng/ml)	AUC_{0-t}* (ng.h/ml)	$AUC_{0-\infty}$* (ng.h/ml)	T_{max}** (h)	$t_{1/2}$** (h)	F**
200 mg IM	3729 (27%)*	10124 (17%)	10465 (17%)	0.54±0.21	6.8±1.7	
300mg Capsule	3817 (36%)	9461 (26%)	10218 (26%)	0.78±0.24	7.8±2.4	0.65±0.09
400mg Cap.	5211 (34%)	12668 (27%)	13647 (28%)	0.73±0.22	7.4±2.0	0.65±0.11
4x100mg Cap.	5198 (30%)	12426 (27%)	13493 (27%)	0.66±0.20	8.0±2.3	0.64±0.11

*Mean (CV%), **Mean±SD.

Test vs. Reference (200mg IM) Geometric Least Squares Means Ratio (90% CI)			
	300mg Capsule	400mg Capsule	4x100mg Capsule
C_{max}	**100.0 (93.9-106.5)**	136.0 (127.7-144.9)	138.0 (129.5-146.9)
AUC_{0-t}	**91.9 (89.5-94.5)**	122.2 (118.9-125.6)	120.1 (116.8-123.4)
$AUC_{0-\infty}$	**96.0 (93.3-98.7)**	127.5 (124.0-131.2)	126.0 (122.5-129.6)

These results indicate that the 300mg oral capsule has C_{max} and $AUC_{0\rightarrow\infty}$ that were comparable to those for the 200mg IM injection (using geometric least squares mean ratios and 90% confidence intervals that all fell within the 80%-125% confidence limit). Subgroup analyses did not reveal any PK effects due to sex or race. Of note, the T_{max} of the 300mg capsule is delayed by about 15 minutes compared to the 200mg IM dose.

The dissolution data submitted indicated th [redacted] The recommended dissolution specification for Tigan 300mg capsule should be [redacted]

Dr. Zhao believes that the submission meets OCPB requirements. It demonstrates that the pharmacokinetics of the 300mg capsule are comparable to those of the 200mg I.M. injection and it addresses the issues raised in the 1/9/1979 Federal Register notice. Therefore, she concludes that the 300mg capsule can be used to replace the 250mg capsules that are currently marketed.

The sponsor has agreed to adopt the dissolution methods and specifications that she outlined in her review. They have also agreed to a phase 4 commitment to provide information regarding the metabolism of trimethobenzamide for labeling purposes.

Dr. Broadbent provides the chemistry review. He finds no outstanding chemistry issues and recommends approval. We consulted OPDRA to review the container labeling of the 100 and 500 count bottles. They made specific labeling recommendations in order to minimize potential user error. The sponsor has agreed to all of these changes.

Discussion

The sponsor has provided the results of a single PK study in healthy male subjects that show that a single 300mg capsule taken orally is comparable from a pharmacokinetic standpoint to the 200mg IM injection, and the OCPB reviewer concurs with this conclusion. This is based on a comparison of C_{max} and AUC. As the team leader for this application, I am unable to conclude from these data; however, that Tigan 300mg, when taken orally in the intended patient population, is effective for its stated indication: nausea and vomiting.

I have two concerns, one minor in this case and the other more significant. First, the T_{max} of the oral formulation is delayed by 50% compared to the IM injection (from about 30 minutes to 45 minutes) and it is not clear how this might affect efficacy. Secondly, it is far from clear to me that patients with symptomatic nausea and vomiting who take oral Tigan 300mg are capable of achieving the exposures seen in this PK study, which was conducted in normal subjects. Simply put, how do we know that a patient with nausea and vomiting will be able to keep an oral capsule down to allow for adequate absorption of the medication? The PK study, as designed and performed, does not address this important question.

Regarding the T_{max} issue, the IM injection has a T_{max} of about 30 minutes. The 300mg capsule has a T_{max} of 45 minutes – a delay of about 50%. Although we don't ordinarily look at T_{max} when evaluating bioequivalence, we as a Division do look at it in situations where we think it might be clinically important. One such situation is when a medication is used to treat a specific symptom acutely. We assume that a delay in absorption of a medication may effect its efficacy in this setting.

Tigan seems similar to in that both are used for the acute treatment of a specific symptom. As a result, we should be concerned about relying strictly on PK data for approval if we see a significant delay in T_{max}. The main question, of course, is what constitutes a significant delay? One important consideration is the time point at which one expects to see efficacy. In the case of migraine, this was two hours, so a delay in T_{max} from 1.5 hours out to 3 hours (past the time point when efficacy is expected) was a significant concern.

In the case of nausea, it's not clear what time point is important for efficacy. I attempted to answer that question by reviewing the labeling of other anti-emetics. The ondansetron labeling describes clinical trials that demonstrated efficacy for the prevention of nausea and vomiting, not its acute treatment. It used the occurrence of nausea/vomiting for 24 hours as the primary endpoint.

It's noteworthy that several other approved oral medications for nausea and vomiting are also studied and indicated for *prevention* (metaclopramide, dolasetron, granisetron). Other medications approved for the actual control of nausea/vomiting do not describe in their labeling how efficacy was established (Marinol, phenergan, compazine, thorazine, perphenazine). Therefore, I'm unable to determine, based on regulatory precedent, how to define what might constitute a significant delay in T_{max}.

Nonetheless, the delay in T_{max} seen in this study is only 15 minutes. I think it is reasonable to assume that this would not affect efficacy to any great extent...it may delay the onset of relief slightly, but probably not significantly.

The larger question remains. How are the PK results obtained in normal subjects applicable to a population of patients with nausea and vomiting? I believe one cannot assume that patients, when administered Tigan orally, will achieve the exposures necessary for efficacy. Many patients with vomiting will likely throw the tablet back up. Patients with nausea likely have significant alteration in gastrointestinal motility, as part of their underlying illness, which would affect absorption. I posit that there is a high likelihood that the PK profile of oral Tigan in patients will differ substantially from that seen in normal healthy subjects.

Therefore, I believe what is needed for approval is

One might entertain other options to approve this application. For example, since patients with vomiting cannot reasonably be expected to keep a capsule down, one might consider approving the oral capsule for the treatment of just nausea alone. I find this problematic for the reason that I previously stated. Patients with nausea often have impaired gastrointestinal motility that can itself impair absorption of oral medications. We certainly see this in migraine, for example, where absorption of triptan medications is often delayed during a migraine attack. It may be that the T_{max} of Tigan in patients with nausea is delayed to such a degree where it *would* become a concern clinically. Short of an actual efficacy study, only the results of a PK study in actual patients can address these concerns.

Another option is to state in labeling th[redacted]). I find this, too, problematic because it violates the intend-to-treat principles. For approval, a medication must be effective in the population that you intend to treat, not in a subgroup of the population that simply tolerates the drug. Furthermore, it ignores the possibility that a patient with nausea may tolerate the drug, but it may not be effective due to a potential clinically significant delay in T_{max}.

Finally, I refer to the agreement between CDER and the sponsor, signed on August 14-16, 2001, which intends to resolve outstanding regulatory issues. As I read it, I don't believe that a non-approval action violates the terms of the agreement. The agreement states:

"Capsules (NDA 17-531). a. King has submitted to FDA a supplement to NDA 17-531, dated February 8, 2001, and received by FDA on February 23, 2001, containing a bioequivalence study intended to support the marketing of a 300 mg Tigan capsule product.

"b. If FDA, after reviewing the supplement, informs King that the supplement does not support the marketing of a 300 mg Tigan capsule product, FDA shall, as it deems appropriate, withdraw approval of NDA 17-531."

I also read the minutes of the meeting held with the sponsor on 12/16/99. This meeting discussed the design of the PK study. The minutes are silent with regard to the study population to be used (healthy subjects vs. patients).

In summary, I conclude that the data available do not support the efficacy of Tigan 300mg capsule in patients with nausea and vomiting. In my opinion, additional study is necessary; therefore, I recommend a non-approval action.

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/s/

Armando Oliva
11/8/01 11:28:59 AM
MEDICAL OFFICER

MEMORANDUM

DATE: December 6, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 17-531

SUBJECT: Recommendation for Action on NDA 17-531, for the reformulation of Tigan (trimethobenzamide HCl) Capsules in fulfillment of a DESI requirement

This application, for the reformulation of Tigan (trimethobenzamide HCl) Capsules in fulfillment of a DESI requirement, was submitted by King Pharmaceuticals on 2/8/01. The history of this product is long and complex.

Briefly, Tigan is currently marketed as 100 and 250 mg capsules, 200 mg IM injection, and 100 and 200 mg suppositories, each indicated to be given TID or QID for the control of nausea and vomiting (the 100 mg dosage strengths are currently indicated for pediatric patients). However, in a Federal Register notice of 1/9/79, the Agency reached the following conclusions:

1) Tigan is effective for the nausea of gastroenteritis, and postoperative nausea and vomiting
2) Certain labeling and marketing conditions must be met, and
3) The 100 and 250 mg capsules were to be reformulated to [redacted] and 400 mg capsules, respectively. This latter requirement was imposed in order to determine if the markedly decreased bioavailability of the oral dosage forms compared to the IM was due to a "first pass" effect, or to a non-optimum formulation.

The same FR notice contained the Agency's conclusion that the suppository dosage form was not effective and proposed the withdrawal of that NDA. The sponsor at that time (Beecham) filed requests for hearings for both the capsule and suppository findings (the notice also contained the Agency's finding that the oral product was not effective for several indications), and the Agency sent the sponsor a letter on 4/19/79 which permitted Beecham to continue to market the suppository pending a ruling on the hearing request. This request has not been acted upon, but the current sponsor (King Pharmaceuticals) has withdrawn the request, pursuant to an agreement signed with the Agency on 8/14,16/01 (see below).

The current application is the result of extensive discussions between the sponsor, the Division, and the Regulatory Policy Staff (Brian Pendelton and David Read). In short, all parties have agreed (via the signed agreement referred to above) that the sponsor could fulfill the requirements outlined in the

1/9/79 FR notice for the oral capsule by formulating an oral dosage form that is bioequivalent to the 200 mg IM injection. For the suppository, the sponsor has agreed to conduct and submit a study or studies demonstrating the effectiveness of a suppository dosage form (dose to be determined). The results of these data must be submitted by 12/2/02. If the data are not submitted by this date (or the data do not support approval), the suppository dosage form will be withdrawn. The agreement also outlines the requirement for the sponsor to submit a supplement intended to support the marketing of an injection dosage form within 30 days of the Agency's decision on the capsule application (this latter is a technical requirement that is intended to ensure that the sponsor submits the new labeling [the three products share the same label] to the injection NDA).

After considerable preliminary work, the sponsor has determined that a 300 mg capsule strength is bioequivalent to the 200 mg IM injection. Accordingly, the application contains the results of a bioequivalence study comparing the 300 mg capsule to the 200 mg IM injection, performed in healthy volunteers. If the Agency finds the data acceptable, this capsule will replace the currently available 100 and 250 mg capsules. In addition, the application contains the relevant CMC information for the capsule.

The application has been reviewed by Dr. Hong Zhao, Office of Clinical Pharmacology and Biopharmaceutics (review dated 9/28/01), Dr. Thomas Broadbent (reviews dated 5/29/01, 7/25/01, 10/12/01, and 11/28/01), and Dr. Armando Oliva, Neurology Team Leader (memo dated 11/8/01).

Drs. Zhao and Broadbent recommend that the application be approved. In particular, the 300 mg capsule has been found to be bioequivalent to the 200 mg IM injection. Dr. Oliva, however, recommends that the application not be approved.

Dr. Oliva raises 2 issues. First, he points out that the Tmax for the capsule is about 50% greater than that of the injection (45 minutes compared to 30 minutes, respectively), and that for an acute treatment, this may be problematic. He ultimately concludes, however, that this difference is not likely to be clinically significant.

The more critical issue, from his point of view, is that he is unsure that the capsule will be bioequivalent to the injection in patients with nausea and/or vomiting, given uncertainties in absorption in this population.

He does offer a potential route to approval, which he ultimately rejects. He suggests that an apparently reasonable approach might be to approve the drug only for those patients who can keep the capsules down. He ultimately rejects this option, however, because in his view it violates the intent-to-treat principle; that is, a drug should be effective in the population for whom it is indicated, not just in a subgroup that tolerates it. Also, in his view, this approach would ignore

the possibility that a patient with only nausea might have a Tmax that could be clinically significantly greater than that of the injection, rendering the product ineffective.

Because of doubts about the effectiveness of the capsule in patients, we asked the sponsor to address these concerns; they responded in a submission dated 12/3/01.

The submission contains an argument that explains, in the sponsor's view, why the GI disturbances associated with nausea and vomiting should not alter the product's effectiveness. These arguments, based on the pKa, the product's solubility, composition, kinetics, and various presumed alterations in the GI tract in patients with nausea and vomiting, suggest to the sponsor that the drug will be well-dissolved in the stomach as well as in the small intestine, that absorption occurs in the stomach as well as the small intestine, and that the changes in the GI tract in patients would not prevent absorption of adequate amounts of drug unless the patient vomited within 30-60 minutes of ingestion.

The sponsor also notes that the Agency has recently approved several generic oral anti-nauseants based on bioequivalence studies performed in healthy volunteers.

I have a few comments.

First, I share Dr. Oliva's view that the greater Tmax of the capsule is not particularly problematic. The product is not an acute treatment in the same way that a migraine treatment is. Tigan is taken BID or TID during a period in which the patient is nauseated and/or vomiting; the drug is not taken to treat a specific acute event. For this reason, the delayed Tmax is considerably less of a concern than it would be for, say, a treatment for an acute migraine headache.

I also find much of the sponsor's argument interesting, suggestive, and even supportive of their conclusion, but by itself not persuasive, given its reliance on conjecture and events not terribly well understood. I also find their point that the Agency has recently approved generic oral anti-emetics on the basis of equivalence in healthy volunteers irrelevant. Specifically, it is appropriate to conclude (as the Agency has in these cases) that 2 oral products that perform the same in healthy volunteers will perform the same in patients with nausea and/or vomiting, regardless of the differences in absorption between the healthy and abnormal states. This similarity between the drugs **within** either of these states (healthy or ill) guarantees that the generic will be effective because the reference drug has been shown to be effective in clinical trials. This situation is not analogous to the Tigan situation.

However, I do find one of the sponsor's arguments persuasive.

Specifically, the sponsor points out that the trials the Agency relied upon to determine the effectiveness of Tigan used oral doses of 200-250 mg TID or QID. Clearly, as the sponsor points out, the levels achieved with the new 300 mg capsule will be greater than those achieved **in patients** at these doses (again, because the 300 mg dose yields plasma levels in healthy subjects greater than those resulting from a 250 mg dose in healthy subjects), and that were shown to be effective in those patients (that the levels are not too high is supported by the demonstration of bioequivalence to the 200 mg IM injection). This permits the conclusion, in my view, that the 300 mg dose will be effective in patients. Further, it appears that the FR requirement to re-formulate the capsule was designed to produce a capsule product that was bioequivalent to the IM injection (or at least determine the reasons for the lack of equivalence), not to produce an effective oral dosage form (this latter had presumably been demonstrated in clinical trials).

Also, I disagree with Dr. Oliva's conclusion that recommending the drug for only those patients who can keep the capsule down violates the intent-to-treat principle.

The intent-to-treat principle is a principle applied to the analysis of clinical trials. I would argue that no drug is effective in all patients who carry the diagnosis for which the drug is indicated, and that, indeed, it makes sense to only prescribe a drug for patients who tolerate it (given, of course, that it has been shown to be effective in some sample with the condition). It seems to me reasonable to expect, for example, that in the clinical trials supporting effectiveness, patients who could not keep the capsules down were not effectively treated (to be sure, the intent-to-treat principle would have dictated that these patients be included in the analysis). This does not subvert the finding that the drug is effective, but it does, in my view, make it reasonable to conclude that the drug will not be effective in patients who cannot keep it down, and that practitioners should evaluate the patient to see if the drug is being kept down. However, this is true for any orally administered drug; if the patient vomits any oral treatment, it is reasonable to conclude that that dose has not been, and cannot be, effective, although the drug may very well be effective in that patient under other circumstances, or in patients generally.

For these reasons, then, I believe the bioequivalence study is relevant.

I should note that the labeling we are recommending be adopted is, with minor changes to include the new formulation and a description of its kinetics, not consistent with current content and format regulations. Given the long marketing history of this product with this labeling, and the difficulties associated with bringing it into conformance with current standards, I believe it can be approved with this label.

Finally, we have asked the sponsor to announce this new dosage strength (and the future unavailability of any other oral dosage strengths) with a Dear Health Care Practitioner letter. We believe that this will be a useful way to inform prescribers about which oral strength they can now prescribe.

For these reasons, then, I recommend that the application be approved.

Russell Katz, M.D.

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/s/

Russell Katz
12/7/01 11:27:13 AM
MEDICAL OFFICER