CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-385

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

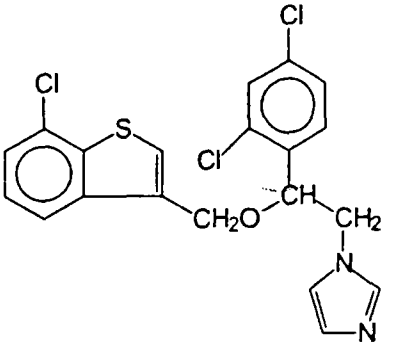
NDA number: 21-385
Review number: 2
Sequence number/date/type of submission: N-000(A2)/letter date October 9, 2003; stamp date October 10, 2003/response to Approvable letter

Information to Sponsor: Yes (x) No ( )
Sponsor and/or agent: Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-431
Manufacturer for drug substances: DPT Laboratories.
307 E. Josephine St.
San Antonio, TX 78215

Reviewer name: David Allen, Ph.D.
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: November 25, 2003

Drug:

Trade name: Sertaconazole nitrate 2%
Generic names (list alphabetically): sertaconzole nitrate 2%
Code name: not provided
Chemical names: (±)-[2, 4-Dichloro-β-[(7-chlorobenzo [*b*] thien-3-yl) methoxy] phenethyl] imidazole nitrate
CAS registry number: 99592-39-9
Mol file number: not provided
Molecular formula/molecular weight: $C_{20}H_{15}Cl_3N_2OS.HNO_3$/500.8
Structure:



Relevant INDs/NDAs/DMFs: IND 50,726
Drug class: antifungal
Indication:

Clinical formulation:

Ingredients	mg/g
Sertaconazole Nitrate	20.0
Ethylene Glycol and Polyethylene Glycol Palmitostearate	
Polyoxyethylene and Glycolized Saturated Glycerides	
Glyceryl Isostearate	
Light Mineral Oil, NF	
Sorbic Acid, NF	
Methylparaben, NF	
Purified Water, USP	
Total	1000.0

Route of administration: topical
Proposed use: From the current label, sertaconazole nitrate 2% is to be applied twice daily for 4 weeks in sufficient amounts to cover both the affected areas between the toes and the immediately surrounding healthy skin of patients with interdigital tinea pedis.
Introduction and drug history: An approvable letter was sent to the Sponsor on July 26, 2002 that detailed several deficiencies that would need to be addressed prior to approval. The only Pharmacology/Toxicology issue was the need for a dermal carcinogenicity study that could be completed as a Phase 4 commitment. The current submission (N-000 A2) is the Sponor's response to the multidisciplinary issues conveyed in the approvable letter.

Studies reviewed within this submission: none

Studies not reviewed within this submission: none

Disclaimer: Tabular and graphical information is from Sponsor's submission unless stated otherwise. Much of the infomation below is excerpted from the review of K Mainigi and/or a subsequent memo by A. Jacobs.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: As stated in the PharmTox review of the original NDA submission, NDA 21-385 (sertaconazole nitrate 2%) is approvable from a nonclinical perspective, with the provision that a Phase 4 commitment is agreed upon by the Sponsor to complete a dermal carcinogenicity study with the to-be-marketed formulation.

B. Recommendation for Nonclinical Studies: An adequate battery of nonclinical studies has been submitted with this NDA to support its approval. However, a Phase 4 dermal carcinogenicity study should be completed to determine the adverse effects to the skin resulting from intermittent chronic exposure (i.e. 6 months over a 10-year period).

C. Recommendations on Labeling: Labeling recommendations were conveyed to the Sponsor in the approvability letter, and all recommended nonclinical portions have been included in the revised labeling provided in the current submission, with one minor exception. The Nursing Mothers section of the label should read as follows: "Nursing Mothers: It is not known if sertaconazole nitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when prescribing [redacted] cream, 2% to a nursing woman."

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: (from the labeling conveyed in the approvable letter dated 7/26/02) Long-term studies to evaluate the carcinogenic potential of sertaconazole nitrate [redacted] have not been conducted. No clastogenic potential was observed in a mouse micronucleus test. Sertaconazole nitrate was considered negative for sister chromatid exchange (SCE) in the *in vivo* mouse bone marrow SCE assay. There was no evidence that sertaconazole nitrate induced unscheduled DNA synthesis in rat primary hepatocyte cultures. Sertaconazole nitrate exhibited no toxicity or adverse effects on reproductive performance or fertility of male or female rats given up to 60 mg/kg/day orally by gastric intubation (16 times the maximum recommended human dose based on a body surface area comparison).

Pregnancy: ***Teratogenic Effects. Pregnancy Category C:*** Oral reproduction studies in rats and rabbits did not produce any evidence of maternal toxicity, embryotoxicity or teratogenicity of sertaconazole at oral doses of 160 mg/kg/day) (40 times (rats) and 80 times (rabbits) the maximum recommended human dose on a body surface area comparison). In an oral peri-postnatal study in rats, a reduction in live birth indices and an increase in the number of still-born pups was seen at 80 and 160 mg/kg. There are [redacted] no adequate and well-controlled studies that have been conducted on topically applied [redacted] in pregnant women. Because animal reproduction studies are not always predictive of human response,

[redacted] should be used during pregnancy only if clearly needed.

B. Pharmacologic Activity: In experimental trichophytosis and dermatomycosis in guinea pig model, sertaconazole exhibited broad-spectrum antifungal activity against dermatophytes and pathogen fungi. It has expressed both fungistatic and fungicidal activities. In the current submission, the Sponsor has provided studies of resistance with sertaconazole that were reported as negative in multiple fungal strains, along with susceptibility tests that report that sertaconazole is at least as effective as clotrimazole and itraconazole. These studies have not been reviewed by the Clinical Microbiology Reviewer.

C. Nonclinical Safety Issues Relevant to Clinical Use: None at this time. The long term effects to the skin resulting from chronic intermittent topical sertaconazole exposure should be evaluated in a dermal carcinogenicity study. As noted in the memo by A. Jacobs, Ph.D., because this product is expected to be used repeatedly for the proposed indication, there should be a phase 4 commitment to conduct a [redacted] dermal carcinogenicity study. This would be consistent with our division practice for this indication. As noted in ICH S1A, "For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed." The need for a dermal carcinogenicity study is guided by the chronic nature or rate of recurrence of the indication and not by systemic absorption of the drug substance or the absence of genotoxicity. A cause for concern is not necessary to support the need for dermal carcinogenicity studies for the tinea pedis indication. The long-term effects of the entire formulation on the skin are of interest. Furthermore, the skin receives large doses of sertaconazole and its vehicle. Sertaconazole is reported to achieve high epidermal concentrations following cutaneous application. Cutaneous absorption was 64% of the dose at 12 hours and 72% at 24 hours following topical application of a 2% cream (Farre M, Ugena B, Badenas JM et al: Pharmacokinetics and tolerance of sertaconazole in man after repeated percutaneous administration. Arzneimittelforschung 1992; 42:752-754). Hyperplasia and hyperkeratosis were seen in the skin of dogs that received 2% sertaconazole cream or vehicle cream for 92 days. This further supports the need for a phase 4 dermal carcinogenicity study.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:
NDA
HFD-540

HFD-540/DivDirector/Wilkin
HFD-540/Deputy DivDirector/Kukich
HFD-540/SupPHARM/Jacobs
HFD-540/ PHARM/Allen
HFD-540/MO/Porres
HFD-540/CHEM/Hathaway
HFD-540/PMS/Cross
C:\data\my documents\NDA Reviews\N21385 \N21385 (N-000 A2)

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Pharmacology summary: In experimental trichophytosis and dermatomycosis in a guinea pig model, sertaconazole exhibited broad-spectrum antifungal activity against dermatophytes and pathogen fungi. It has expressed both fungistatic and fungicidal activities. In the current submission, the Sponsor has provided studies of resistance with sertaconazole that were reported as negative in multiple fungal strains, along with susceptibility tests that report that sertaconazole is at least as effective as clotrimazole and itraconazole. These studies have not been reviewed by the Clinical Microbiology Reviewer.

Pharmacology conclusions: No new nonclinical pharmacology studies are necessary to support the approval of this NDA.

II. SAFETY PHARMACOLOGY:

Safety pharmacology summary: According to the original review of NDA 21-385, at concentrations much higher than the proposed clinical dose, sertaconazole nitrate did not affect the cardiovascular, neurologic, or pulmonary functions in adult rodents.

Safety pharmacology conclusions: No new nonclinical safety pharmacology studies are necessary to support the approval of this NDA.

III. PHARMACOKINETICS/TOXICOKINETICS:

Absorption: Data obtained from single and multiple-dose, multispecies pharmacokinetic studies indicated that the maximal topical absorption of 2% sertaconazole nitrate cream was 18% of the applied dose. In other dermal studies involving different formulations of sertaconazole nitrate, the systemic absorption ranged from 0.7% for powder to about 2% for solution, the values for cream and gel were 1.5 and 0.9%, respectively. The percent absorption in rats following an oral dose reached 48%. However, sertaconazole is reported to achieve high epidermal concentrations following cutaneous application. Cutaneous absorption was 64% of the dose at 12 hours and 72% at 24 hours following topical application of a 2% cream (Farre M, Ugena B, Badenas JM et al: Pharmacokinetics and tolerance of sertaconazole in man after repeated percutaneous administration. Arzneimittelforschung 1992; 42:752-754).

Distribution: In various dermal studies, very low amounts of drug and its metabolites (as measured by a microbiological assay) were found in the plasma, liver, and kidney, indicating a rapid hepatic metabolism. Low levels of drug were also found in a rat study where animals received 20mg sertaconazole nitrate/kg via the intravenous, subcutaneous, and oral routes. At 6-hours post-dose, the plasma drug levels for three routes were 0.9, 1.0, and 0.63µg/mL, respectively.

Metabolism: In rats, low dermal bioavailability of 0.48% indicated rapid metabolism. The low oral bioavailability (48%) in rats receiving 10mg sertaconazole nitrate/kg also confirmed rapid metabolism. Most of the plasma radioactivity was attributed to the inactive metabolites. The Tmax was achieved at 1.23 post-dose hours. The half-life in rats following the intravenous dose (10mg/kg) was approximately 5 hours. It was suggested that the high levels of radioactivity in the liver compared with blood and kidneys indicated a broad hepatic metabolism. In a 26-week oral (15, 60, and 240mg sertaconazole nitrate/kg/day) study in rats, the terminal plasma levels and AUC values in females were higher than males. As evident from the Tmax (females 1-hour, males 2-8 hours), the absorption of drug was also more rapid in females. In addition, the Tmax in males was dose dependent. It should be noted the metabolites have not been characterized.

Excretion: Irrespective of the route of administration, elimination occurred predominantly through the bile. In rats receiving intravenous dose of 10mg/kg of ^{14}C-sertaconazole nitrate, approximately 91% of radioactivity appeared in the bile and within 4 hours more than 80% of the radioactivity was eliminated, with 90% eliminated by 24 hours. The recovery of parent drug was minimal. Four inactive metabolites were identified by microbiological assay. At 20 and 50mg/kg intravenous doses, urine contained 0.035 and 0.043% of the administered radioactivity, respectively.

PK/TK conclusions: No new nonclinical PK/TK studies are warranted to support approval of this NDA.

IV. GENERAL TOXICOLOGY:

Toxicology summary: The acute, subchronic, and chronic toxicity studies conducted in several species at dose levels much greater than the maximum recommended clinical dose did not reveal any significant irreversible adverse effects. As determined by acute oral, subcutaneous and intraperitoneal doses of sertaconazole nitrate to mice and rats, the LD_{50} exceeded 2g/kg. In these studies, no significant toxicity was observed. In an intraperitoneal study in mice, only 3% of the animals died at 8g/kg dose of sertaconazole nitrate.

In a 4-week dermal study in rabbits, no drug related systemic or local toxicity was observed at 100mg/kg-dose level.

In three-month dermal toxicity studies in rats and dogs (10, 20, and 40mg sertaconazole/kg/day) conducted with the 2% cream formulation, incidence of minimal to slight irritation (acanthosis, hyperkeratosis, mixed inflammatory cell infiltrate) was observed in all the treatment groups including controls. No systemic toxicity was observed in either species, and thus the NOEL for systemic toxicity was considered to be greater than 40mg/kg/day.

In a 26-week oral rat study (15, 60, and 240mg/kg/day), minimal signs of toxicity indicated by ptyalism, increased liver weights, hepatocellular hypertrophy along with intracytoplasmic concentric bodies, were observed at the mid- and high-dose levels. Four deaths occurred at the high-dose level. None of the findings were sex or dose related. The NOEL was considered to be 15mg/kg/day.

In a 26-week oral dog study (7.5, 30, and 120mg/kg/day), no signs of systemic toxicity were observed at the low- and mid-dose levels. Although reduced body weight gains occurred at the high-dose level, the body weight gains were similar in all the treatment groups during the 8-weeks recovery period.

Toxicology conclusions: No additional nonclinical toxicology studies are warranted to support the approval of this NDA.

V. GENETIC TOXICOLOGY:

Genetic toxicology summary: See labeling recommendations below which have been incorporated into the revised label in the current submission.

Genetic toxicology conclusions: No additional genetic toxicology studies are warranted to support the approval of this NDA. However, as noted in the memo by A. Jacobs, although adequate tests for clastogenicity have been conducted, adequate tests of mutagenicity have not been conducted.

Labeling recommendations: No clastogenic potential was observed in a mouse micronucleus test. Sertaconazole nitrate was considered negative for sister chromatid exchange (SCE) in the *in vivo* mouse bone marrow SCE assay. There was no evidence that sertaconazole nitrate induced unscheduled DNA synthesis in rat primary hepatocyte cultures.

VI. CARCINOGENICITY:

Carcinogenicity summary: No carcinogenicity studies have been submitted to this NDA. The current submission contains a response from the Sponsor to the PharmTox recommendation for a Phase 4 dermal carcinogenicity study included in the approvability letter. The Sponsor has requested that this commitment be removed based on the anticipated duration of use, and the absence of carcinogenic signals (e.g. genotoxicity) in nonclinical toxicology studies submitted with this NDA. The Sponsor states that sertaconazole is intended to be used only 4 weeks, and that intermittent use is not anticipated to be chronic (although they do state that tinea pedis may recur in some patients throughout the patient's lifetime). The Sponsor also states that none of the members of the imidazole class of antifungals have been associated with tumor formation or genetic damage. The Sponsor states that none of the subchronic and chronic nonclinical studies with sertaconazole revealed "precancerous" effects. The Sponsor references approved labeling for other antifungals that indicate that carcinogenicity testing has not been previously required.

Carcinogenicity conclusions: The long term effects to the skin resulting from chronic intermittent topical sertaconazole exposure should be evaluated in a dermal carcinogenicity study. As noted in the memo by A. Jacobs, Ph.D., because this product is expected to be used repeatedly for the proposed indication, there should be a phase 4 commitment to conduct a dermal carcinogenicity study. This would be consistent with our current division practice for this indication. As noted in ICH S1A, "For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed." The need for a dermal carcinogenicity study is guided by the

chronic nature or rate of recurrence of the indication and not by systemic absorption of the drug substance or the absence of genotoxicity. A cause for concern is not necessary to support the need for dermal carcinogenicity studies for the tinea pedis indication. The long-term effects of the entire formulation on the skin are of interest. Furthermore, the skin receives large doses of sertaconazole and its vehicle. Sertaconazole is reported to achieve high epidermal concentrations following cutaneous application. Cutaneous absorption was 64% of the dose at 12 hours and 72% at 24 hours following topical application of a 2% cream (Farre M, Ugena B, Badenas JM et al: Pharmacokinetics and tolerance of sertaconazole in man after repeated percutaneous administration. Arzneimittelforschung 1992; 42:752-754). Hyperplasia and hyperkeratosis were seen in the skin of dogs that received 2% sertaconazole cream or vehicle cream for 92 days. This further supports the need for a phase 4 dermal carcinogenicity study.

Labeling Recommendations: Long-term studies to evaluate the carcinogenic potential of sertaconazole nitrate ——— have not been conducted.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproductive and developmental toxicology summary: See the labeling recommendations below which have been incorporated into the revised label in the current submission.

Reproductive and developmental toxicology conclusions: Additional nonclinical reproductive and developmental toxicology studies are not necessary to support the approval of this NDA.

Labeling recommendations: Sertaconazole nitrate exhibited no toxicity or adverse effects on reproductive performance or fertility of male or female rats given up to 60 mg/kg/day orally by gastric intubation (16 times the maximum recommended human dose based on a body surface area comparison).

Pregnancy: ***Teratogenic Effects. Pregnancy Category C:*** Oral reproduction studies in rats and rabbits did not produce any evidence of maternal toxicity, embryotoxicity or teratogenicity of sertaconazole at oral doses of 160 mg/kg/day) (40 times (rats) and 80 times (rabbits) the maximum recommended human dose on a body surface area comparison). In an oral peri-postnatal study in rats, a reduction in live birth indices and an increase in the number of still-born pups was seen at 80 and 160 mg/kg. There are ——— no adequate and well-controlled studies that have been conducted on topically applied ——— in pregnant women. Because animal reproduction studies are not always predictive of human response, ——— should be used during pregnancy only if clearly needed.

VIII. SPECIAL TOXICOLOGY STUDIES:

No new special toxicology studies are warranted to support the approval of this NDA.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: The Sponsor provided a complete response to the approval issues listed in the Agency's approvable letter. However, they have expressed their unwillingness to commit to a

Phase 4 dermal carcinogenicity study. Consistent with current Division practices, this study should still be recommended.

Labeling recommendations were conveyed to the Sponsor in the approvability letter, and all recommended nonclinical portions have been included in the revised labeling provided in the current submission, with one minor exception. The Nursing Mothers section of the label should read as follows: "Nursing Mothers: It is not known if sertaconazole [redacted] is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when prescribing [redacted] to a nursing woman."

General Toxicology Issues: No new toxicology issues have been identified in the current submission.

Recommendations for Phase 4: Because this product is expected to be used repeatedly for the proposed indication (≥ 6 months of treatment over a 10-year period), a phase 4 commitment to conduct a [redacted] dermal carcinogenicity study is recommended. This would be consistent with our current division practice for this indication. As noted in ICH S1A, "For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed." The need for a dermal carcinogenicity study is guided by the chronic nature or rate of recurrence of the indication and not by systemic absorption of the drug substance or the absence of genotoxicity.

The following information was conveyed to the Sponsor in the Approval Action Letter on November 25, 2003:
Commitment/Study Description: Conduct a dermal carcinogenicity study. The need for a dermal carcinogenicity study is guided by the chronic nature or rate of recurrence of the indication and not by systemic absorption of the drug substance or the absence of genotoxicity. (ICH S1A, "For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed.").

Protocol Submission:	by March 10, 2004.
Study start:	by December 10, 2004
Final report submission:	by December 10, 2007

Labeling with basis for findings:
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies to evaluate the carcinogenic potential of sertaconazole nitrate have not been conducted. No clastogenic potential was observed in a mouse micronucleus test. Sertaconazole nitrate was considered negative for sister chromatid exchange (SCE) in the *in vivo* mouse bone marrow SCE assay. There was no evidence that sertaconazole nitrate induced unscheduled DNA synthesis in rat primary hepatocyte cultures. Sertaconazole nitrate exhibited no toxicity or adverse effects on reproductive performance or fertility of male or female rats given up to 60 mg/kg/day orally by gastric intubation (16 times the maximum recommended human dose based on a body surface area comparison).

Pregnancy: ***Teratogenic Effects. Pregnancy Category C:*** Oral reproduction studies in rats and rabbits did not produce any evidence of maternal toxicity, embryotoxicity or teratogenicity of

sertaconazole nitrate at an oral dose of 160 mg/kg/day (40 times (rats) and 80 times (rabbits) the maximum recommended human dose on a body surface area comparison). In an oral peri-postnatal study in rats, a reduction in live birth indices and an increase in the number of still-born pups was seen at 80 and 160 mg/kg/day.

There are no adequate and well-controlled studies that have been conducted on topically applied ERTACZO™ Cream, [redacted], in pregnant women. Because animal reproduction studies are not always predictive of human response, ERTACZO™ Cream, [redacted], should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known if sertaconazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when prescribing ERTACZO™ Cream, [redacted] to a nursing woman.

X. APPENDIX/ATTACHMENTS:

Addendum to review:

Other relevant materials (Studies not reviewed, appended consults, etc.):

Any compliance issues:

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

/s/

David G. Allen
11/26/03 09:39:48 AM
PHARMACOLOGIST

Abby Jacobs
11/26/03 09:51:58 AM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL

INTEGRATED SUMMARY OF EFFICACY

The ISE is located in Volume 1.27 at page 8-2-294 and following.

INTEGRATED SUMMARY OF SAFETY

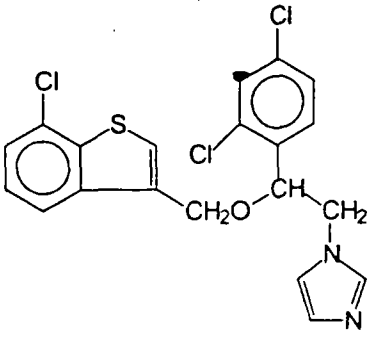
The ISS is located in Volume 1.27 at page 8-2-416 and following.

PHARMACOLOGY/TOXICOLOGY/COVER SHEET

NDA number: 21-385
Review number: 01
Sequence number/date/type of submission: 000/09-28-2001/commercial NDA
IND number: 50, 726
Review number: 03
Sequence number/date/type of submission: 013/03-30-2000/commercial IND
Information to sponsor: **None**
Sponsor and /or agent: Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Manufacturer for [redacted]

Reviewer name: Kumar D. Mainigi
Division name: Division of Dermatologic and Dental Drug Products
HFD# 540
Review completion date:

Drug: **Sertaconazole Nitrate Cream, 2%**
Trade name: Not assigned
Generic name:
Code name: FI-7056
Chemical Name: (±)-[2, 4-Dichloro-β-[(7-chlorobenzo [*b*] thien-3-yl) methoxy] phenethyl] imidazole nitrate
CAS registry number: 99592-39-9
Mol file number:
Molecular formula/molecular weight: $C_{20}H_{15}Cl_3N_2OS.HNO_3$/500.8
Structure:



HNO_3

Relevant INDs/NDAs/DMFs: IND 50, 726

Drug class: Antifungal

Indication: Treatment of interdigital tinea pedis caused by dermatophytes

Clinical formulation:

Ingredients	Mg/Gram
Sertaconazole Nitrate	20.0
Ethylene Glycol and Polyethylene Glycol Palmitostearate	
Polyoxyethylene and Glycolized Saturated Glycerides	
Glyceryl Isostearate	
Light Mineral Oil, NF	
Sorbic Acid, NF	
Methylparaben, NF	
Purified Water, USP	
Total	1000.0

Route of administration: Topical

Proposed use:

Disclaimer: Tabular and graphical information is from sponsor's submissions unless stated otherwise.

Studies reviewed within this submission:

1. Three-month dermal study in rats
2. Sister chromatid exchange assay
3. Unscheduled DNA synthesis assay
4. Segment III oral study in rats
5. Segment I oral study in rats
6. Dermal mouse autoradiography
7. Oral mouse autoradiography
8. Subcutaneous mouse autoradiographic study

Studies submitted but not reviewed within this submission: None

Studies reviewed in previous submissions:

Pharmacodynamics

1. Effects on rat cardiovascular and respiratory systems.
2. Effect on behavior of mice.

Pharmacology

3. Therapeutic effect on dermatomycosis in guinea pigs (I).
4. Therapeutic effect on dermatomycosis in guinea pigs (II).
5. Comparative therapeutic effects of several antifungal agents.
6. Cutaneous retention time test in guinea pigs (I).
7. Cutaneous retention time test in guinea pigs (II).
8. Cutaneous retention time test in guinea pigs (III).
9. Healing effect in guinea pigs (I).
10. Healing effect in guinea pigs (II).
11. Effect on vaginal candidiasis in mice.
12. Anti-inflammatory activity of Sertaconazole.

Biodisposition

13. Dermal absorption of Sertaconazole in rats.
14. Vaginal absorption of Sertaconazole.
15. Absorption of Sertaconazole in rats after oral, intravenous, vaginal administrations.
16. Absorption of Sertaconazole in rabbits after oral, intravenous, and vaginal administrations.
17. Absorption in hairless rats after dermal and intravenous administrations.
18. Plasma drug levels in rats following intravenous, oral, and subcutaneous administrations.
19. Pharmacokinetics in rats following oral administration.
20. Pharmacokinetics in rats following intravenous administration.
21. Urinary and biliary excretion in rats following intravenous administration.
22. Biliary excretion in rats following intravenous drug administration.

Toxicology

Acute Toxicity

23. Acute intraperitoneal toxicity in mice.
24. Acute intraperitoneal toxicity in rats.
25. Acute subcutaneous toxicity in mice.

26. Acute subcutaneous toxicity in rats.

Subchronic Toxicity

27. Twenty-eight day dermal study in rabbits.

Chronic Toxicity

28. Twenty-six week oral toxicity study in rats.
29. Twenty-six week oral toxicity study in dogs.

Tolerance

30. Primary dermal irritation in rabbits.
31. Sensitization in guinea pigs.

Genotoxicity

32. Ames assay.
33. Mice micronucleus assay.

Reproductive and Developmental Toxicity

34. Oral teratogenicity study in rats
35. Oral teratogenicity study in rabbits.

Executive Summary

I. Recommendations

A. **Recommendation on Approvability**: From the non-clinical point of view this new drug application is approvable.

B. **Recommendation for Nonclinical Studies**: All the essential non-clinical studies were conducted, and the profile is complete. No additional studies are required. In a pre-NDA meeting on October 18, 2000, the sponsor was informed about it.

C. **Recommendations for Labeling:** All essential data for labeling are available, and the non-clinical portion of the label is approvable.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings:

A spectrum of pharmacokinetic and autoradiographic studies have indicated that the systemic absorption of drug in rodents never exceeded 18% of the administered dose, and drug is rapidly metabolized and excreted mostly through bile, therefore, its chances of accumulation are negligible. In comparison, only 0.5% of the administered dose was absorbed through the human skin, providing a very wide margin of safety.

In more than two dozens of toxicity studies conducted at fairly large appropriate dose levels using multiple routes in several species, did not reveal any significant irreversible adverse effects. The cream formulation is slightly irritating to animals; however, in humans it did not cause any contact photoallergy or dermal sensitization.

Sertaconazole nitrate did not cause any maternal toxicity, embryotoxicity, or teratogenicity in rats and rabbits (up to160mg/kg/day; margin of safety 230 times in terms of body weight, and 40-80 times greater in terms of body surface). It also did not exhibit any effect on fertility, implantation to early embryonic development. In a peri- and postnatal rat study, a slight but statistically insignifcant decrease in live births was observed at the mid- (4%) and high-dose (7%) levels; an increase in the stillborn pups observed at the mid- (21%, non-significant) and high-dose (33% at $p<0.01$) levels occurred at 121-242 times the maximum recommended clinical dose of 0.66mg/kg (20-40 times in mg/m^2). In a battery of assays, sertaconazole tested non-mutagenic and nonclastogenic.

In clinical studies, drug product did not cause any phototoxicity, but exhibited potential to induce contact dermal photoallergy or contact dermal sensitization.

Sertaconazole nitrate is resistant to photodegradation. Sertaconazole nitrate has been marketed as an antifungal agent in cream, gel, powder, and solution formulations in several European, South and Central American countries under the brand names Dermofix (Ferrer), Zolain (Roberts), and Dermoseptic (Smith Kline Beecham). To date, no serious adverse effects or proliferative dermal lesions raising health concerns have been reported.

Taking into account the pharmacokinetic, toxicologic, genotoxic, and epidemiologic profiles of sertaconazole nitrate, chemical and photocarcinogenicity studies are not warranted.

B. Pharmacologic Activity: In experimental trichophytosis and dermatomycosis in guinea pig model, sertaconazole exhibited broad-spectrum antifungal activity against dermatophytes and pathogen fungi. It has expressed both fungistatic and fungicidal activities.

D. Nonclinical Safety issues Relevant to Clinical use: None

III. Administrative

A. Reviewer signature:----------

B. Supervisor's signature:---------- Concurrence----------

Non-Concurrence--------
(See memo attached)

C.cc:list:

TABLE OF CONTENTS-PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY: No new studies were conducted.

Pharmacology summary/conclusions: In the standard laboratory tests (e.g. experimental trichophytosis and dermatomycosis in guinea pigs, cutaneous retention time test etc.), sertaconazole exhibited broad-spectrum antifungal activity against dermatophytes, and pathogen fungi. It has expressed both fungistatic and fungicidal activites. It is suggested that sertaconazole can block morphogenesis in *C. albicans* by inhibiting the conversion of blastospores to psuedohyphae. Like other imidazole antifungals, sertaconazole also inhibit the fungal/-cytochrome P450 enzyme lanostrol 14-demethylase and thus impair ergosterol synthesis leading to a cascade of membrane abnormalities in fungus. This way the structure and functioning of the cell membrane is affected and its growth is restricted. In a rat croton oil model, 2% sertaconazole nitrate exhibited anti-inflammatory activity.

II SAFETY PHARMACOLOGY: No new studies were conducted.

Neurological effects: A slight change in the behavior of mice at 1g/kg oral dose, and 300mg/kg intraperitoneal dose was observed; it included motor incoordination and increased defecation. In the rat croton oil test, 2% sertaconazole nitrate exhibited significant anti-inflammatory activity by substantial reduction in edema (~40%).

Cardiovascular effects: In a set of studies, the effects of sertaconazole nitrate on the functioning of cardiovascular and pulmonary systems were examined in the adult Sprague-Dawley rats. In a dose escalating (0.625, 1.25, 2.5, and 5mg/kg) intravenous study, no changes in systolic, diastolic and mean blood pressures and heart rate were observed. Similar results were observed at an oral dose of 100mg/kg.

Pulmonary effects: In an intravenous dose escalating (0.625, 1.25, 2.5, and 5.0mg/kg) rat study, sertaconazole did not affect the respiratory flow and rate in anesthetized animals evaluated for 2 hours after the drug administration.

Renal effects: The renal functions were not tested.

Gastrointestinal effects: No studies were conducted to examine such effects.

Abuse liability: None

Other:

Safety pharmacology summary/conclusions: At concentrations much higher than the proposed clinical dose (~0.7mg/kg/day), sertaconazole nitrate did not affect the cardiovascular, neurologic, or pulmonary functions in adult rodents.

III. PHARMACOKINETICS/TOXICOKINETICS: No new studies were conducted.

PK parameters: In various studies, the following parameters were determined: AUC, Cmax, Tmax, MRT, $T_{1/2}$, elimination rate constant, distribution rate constant, and bioavailability etc.

Absorption: Data obtained from a dozen of single and multiple-dose, multispecies pharmacokinetic studies indicated that the topical absorption of 2% sertaconazole nitrate cream never exceeded 18% of the applied dose. The percent absorption via the vaginal route was also similar in rats. In other dermal studies involving different formulations of sertaconazole nitrate, the systemic absorption ranged from 0.7% for powder to about 2% for solution, the values for cream and gel were 1.5 and 0.9%, respectively. The absorption in rats following an oral dose reached 48% with a Cmax of about 0.4%.

Distribution: In various dermal studies, very low amounts of drug and its metabolites (as measured by a microbiological assay) were found in the plasma, liver, and kidney, indicating a rapid hepatic metabolism. Low levels of drug were also found in a rat study where animals received 20mg sertaconazole nitrate/kg via the intravenous, subcutaneous, and oral routes. At 6-hours post-dose, the plasma drug levels for three routes were 0.9, 1.0, and 0.63µg/mL, respectively.

Metabolism: In rats, low dermal bioavailability of 0.48% indicated rapid metabolism. The low oral bioavailability (48%) in rats receiving 10mg sertaconazole nitrate/kg also confirmed rapid metabolism. Most of the plasma radioactivity in this case was attributed to the inactive metabolites. The Tmax was achieved at 1.23 post-dose hours. The apparent half-life in rats following the intravenous dose (10mg/kg) was about 5 hours. It was suggested that the high levels of radioactivity in the liver compared with blood and kidneys indicated a broad hepatic metabolism. In a 26-week oral (15, 60, and 240mg sertaconazole nitrate/kg/day) study in rats, the terminal plasma levels and AUC values in females were higher than males. As evident from the Tmax (females 1-hour, males 2-8 hours), the absorption of drug was also more rapid in females. In addition, the Tmax in males was dose dependent. It must be mentioned that no attempt was made to characterize the metabolites.

Excretion: Irrespective of the route of administration, major elimination occurred through the bile. In rats receiving intravenous dose of 10mg/kg of ^{14}C-sertaconazole nitrate, approximately 91% of radioactivity appeared in the bile and within 4 hours more than 80% of the radioactivity was eliminated and 90% was eliminated within 24 hours. The recovery of parent drug was minimal. Four inactive metabolites were identified by microbiological assay. At 20 and 50mg/kg intravenous doses, urine contained 0.035 and 0.043% of the administered radioactivity, respectively.

PK/TK summary and conclusions: In a nutshell, the pharmacokinetic profile of sertaconazole nitrate has revealed a limited dermal absorption, insignificant tissue accumulation, and rapid metabolism and excretion.

IV. GENERAL TOXICOLOGY:

1. Study title: Sertaconazole: A subchronic (3-month) dermal toxicity study in the rat.

Key study findings: Under the study conditions, sertaconazole nitrate was well tolerated. NOEL was considered to be 40mg/kg/day.

Study no: TSERT-9708
Volume #, and page #: 7, 5-2-144
Conducting laboratory and location: [redacted]
Date of study initiation: July 9, 1997
GLP compliance: Yes
QA report: Yes
Drug, lot #, radiolabel, and % purity: Lot # PLCEA69/not radiolabeled/purity100%
Formulation/vehicle: Sertaconazole nitrate cream, 2%/Placebo cream

Methods (unique aspects): None

Dosing:

Species/strain: Albino rats (outbred) VAF/Plus
#/sex/group or time point (main study): 10/sex/dose group
Satellite groups used for toxicokinetics or recovery: None
Age: 6 weeks
Weight: Males 223g (202-244g); Females 157g (145-177g)
Doses in administered units: 10, 20, and 40mg sertaconazole nitrate kg/day
Route, form, volume, and infusion rate: Topical, cream, 0.5, 1.0, and 2.0 mL/ kg/day

Observations and times:

Clinical signs: Twice daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Pretest, and on test day 90
EKG: None
Hematology /Clinical chemistry: Blood samples were collected at study termination on Day 91 from 5 rats/sex/group
Urinalysis: None
Gross pathology: At study termination
Organs weighed: Brain, kidneys, liver, ovaries, and testes
Histopathology: Examinations were conducted only in the control and high-dose animals.

Histopathology Inventory for NDA #21-385

Study #TSERT-9708			
Species Rat	Examined	Weighed	
Adrenals	X		
Aorta	X		
Bone Marrow smear	X		
Bone (femur)	X		
Brain	X	X	
Cecum	X		
Cervix			
Colon			
Duodenum			
Epididymis			
Esophagus	X		
Eye	X		
Fallopian tube			
Gall bladder			
Gross lesions			
Harderian gland			
Heart	X		
Ileum			
Injection site			
Jejunum			
Kidneys	X	X	
Lachrymal gland	X		
Larynx			
Liver	X	X	
Lungs	X		
Lymph nodes, cervical			
Lymph nodes mandibular			
Lymph nodes, mesenteric	X		
Mammary Gland	X		
Nasal cavity	X		
Optic nerves			
Ovaries	X	X	
Pancreas	X		
Parathyroid			
Peripheral nerve			
Pharynx			
Pituitary	X		
Prostate			
Rectum			
Salivary gland	X		
Sciatic nerve	X		
Seminal vesicles			
Skeletal muscle	X		
Skin	X		

Spinal cord	X	
Spleen	X	
Sternum		
Stomach	X	X
Testes	X	
Thymus	X	
Thyroid	X	
Tongue		
Trachea	X	
Urinary bladder	X	
Uterus	X	
Vagiña		
Zymbal gland		

Toxicokinetics: None
Other: None

Results:

Mortality: One male control rat was found dead on day 14, rest survived till the scheduled sacrifice.
Clinical signs: No drug related signs of systemic toxicity were observed. Slight dermal irritation (erythema, edema, eschar, and necrosis) was observed in all groups during week 1; a decrease in severity of irritation was observed after week 5.
Body weights: No statistically significant inter-group differences were observed.
Food consumption: No statistically significant inter-group differences were observed.
Ophthalmoscopy: No drug and or vehicle related ocular lesions were recorded.
Electrocardiography: N/A
Hematology: Drug and or vehicle did not affect any of the determined parameters.
Clinical chemistry: No inter-group differences were observed.
Urinalysis: N/A
Organ weights: In males liver to body weight, and liver to brain weights were increased by 8 and 16%, respectively.
Gross pathology: No drug or vehicle related macroscopic lesions were observed. No explanation was offered for the death of a control rat on day 14.
Histopathology: Slight to minimal dermal lesions such as acanthosis, hyperkeratosis, and scanty mixed inflammatory cell infiltrate below the epidermis were observed in all the treatment groups including controls.
Toxicokinetics: N/A

Summary of individual study findings: Except for the low gain in body weight at the high-dose level, no other signs of toxicity were observed. At the end of the treatment period, no intergroup differences in gain in body weight were observed.

Toxicology summary/conclusions: The acute, subchronic, and chronic toxicity studies conducted in several species at dose levels much greater than the maximum recommended clinical dos did not reveal any significant irreversible adverse effects. As determined by acute oral, subcutaneous and intraperitoneal doses of sertaconazole nitrate to mice and rats, LD_{50}

exceeded 2g/kg. In these studies, no organ or function related toxicity was observed. In an intraperitoneal study in mice, only 3% of the animals died at 8g/kg dose of sertaconazole nitrate.

In a 4-week dermal study in rabbits, no drug related systemic or local toxicity was observed at 100mg/kg-dose level.

In three-month dermal toxicity studies in rats and dogs (10, 20, and 40mg sertaconazole/kg/day) conducted with 2% cream formulation, incidence of minimal to slight irritation (acanthosis, hyperkeratosis, mixed inflammatory cell infiltrate) was observed in all the treatment groups including controls. No systemic toxicity was observed in either of the species, therefore, NOEL for systemic toxicity was considered to be greater than 40mg/kg/day.

In a 26-week oral rat study (15, 60, and 240mg/kg/day), minimal signs of toxicity indicated by ptyalism, increased liver weights, hepatocellular hypertrophy together with intracytoplasmic concentric bodies, were observed at the mid- and high-dose levels. Four deaths occurred at the high-dose level. None of the findings were sex or dose related. NOEL was considered to be 15mg/kg/day.

In a 26-week oral dog study (7.5, 30, and 120mg/kg/day), no signs of systemic toxicity were observed at the low- and mid-dose levels. Although a low gain in body weight occurred at the high-dose level, the gain in body weight was similar in all the treatment groups during the 8-weeks recovery period.

V. GENETIC TOXICOLOGY:

2. Study title: Mutagenicity test on sertaconazole nitrate in an *in vivo* sister chromatid exchange assay.

Key findings: Sertaconazole nitrate did not cause any cellular cytotoxicity, or induce sister chromatid exchange (SCE).

Study no: 18232-0-458
Study type (if not reflected in title):
Volume #, and page #: 16/5-11-238
Conducting laboratory and location: [redacted]
Date of study initiation: 01-28-1997
GLP compliance: Yes
QA reports: Yes
Drug, lot #, radiolabel, and % purity: Lot# C-1003, 100% purity
Formulation/vehicle: Sertaconazole nitrate in 0.50% aqueous methylcellulose suspension

Methods:

Strains/species/cell line: 8 weeks old Crl:CD-1 (ICR) BR male (25-33g) and female (21-26g) mice
Dose selection criteria: Based on LD_{50} of 8g/kg in mice of the same strain.
Basis of dose selection: A preliminary SCE assay was conducted.

Range finding studies: A preliminary study was conducted at dose levels of 1250, 2500, and 5000mg sertaconazole nitrate/kg.

Test agent stability: Stable for 6 months
Metabolic activation system: N/A
Controls:
Vehicle: 0.5% aqueous methylcellulose suspension
Negative control: Vehicle
Positive control: Cyclophosphamide (10mg/kg)
Comments: The dose selection for the dose range-finding studies was based on LD_{50}
Exposure conditions: N/A
Incubation and sampling times: N/A
Doses used in definitive study: 4000, 4500, and 5000mg sertaconazole nitrate/kg

Study design: To provide continuous exposure to 5-bromodeoxyuridine, five 50mg BrdUrd pellets were subcutaneously implaned in each animal. After one hour, animals (5/sex/dose level) were administered the test doses of vehicle, drug, or positive control. At 24 hours post-treatment, animals were sacrificed, and the extracted bone marrow was processed to obtain cells. Cells fixed on the slides were stained by . technique.

Analysis:
No.of replicates: 25 cells/animal were analyzed for SCEs.
Counting method: The total number of changes based on the dark to light and light to dark areas along the chromatid was considered as the number of SCEs per chromosome. For cell proliferation kinetics, Average Generation Time (AGT) was determined by using the equation: hours of exposure to Brdurd/sum of M_1, M_2, and M_3 cells/100

Criteria for positive results: A statistically significant increase in SCEs in both the sexes.

Summary of individual study findings:

Study validity: A statistically significant increase in SCE was recorded in both sexes treated with the positive control (table).

Sister chromatid exchange and AGT Data

Group	SCE/cell (Mean±SE)		AGT (Mean)	
	Males	Females	Males	Females
Vehicle	3.9±0.4	4.1±0.4	13.6	15.0
Positive control	14.4±1.0*	18.1±1.1*	15.9	14.8
Low-dose	4.6±0.4	5.4±0.5	14.6	14.0
Mid-dose	4.1±0.4	3.2±0.4	14.1	16.9
High-dose	4.6±0.4	4.6±0.3	15.8	14.9

AGT (average generation time)=Hrs.of BurdUrd exposure/M1+M2+M3/100

*Significantly greater than the vehicle control, p>0.05

Study outcome: Sertaconazole nitrate was not cytotoxic to the bone marrow of males or females as evident by similar AGT values at all dose levels. The SCEs count in both sexes was similar to the vehicle control at all dose levels. Under the assay conditions, sertaconazole nitrate did not induce SCE induction or cause cellular cytotoxicity.

3. Study title: Genotoxicity test on sertaconazole nitrate in the *in vivo/in vitro* unscheduled DNA synthesis in rat primary hepatocytes cultures at two timepoints.

Key findings: Sertaconazole was inactive in inducing the unscheduled DNA synthesis (UDS) in rat primary hepatocyte cultures.

Study no: 18232-0-494
Study type (if not reflected in title)**:**
Volume #, and page #: 16, 5-11-298
Conducting laboratory and location: [redacted]
Date of study initiation: 01-08-1997
GLP compliance: Yes
QA reports: Yes
Drug, lot #, radiolabel, and % purity: Lot # C-1003, purity 100%

Formulation/vehicle: Sertaconazole nitrate in 0.5% aqueous methylcellulose suspension

Methods:

Strains/species/cell line: Fischer-344/rat/ primary hepatocytes
Dose selection criteria:
Basis of dose selection: Dose range-finding study
Range finding studies: 20, 100, 500, 1000, and 2000mg/kg
Test agent stability: Stable for 6 months
Metabolic activation system: N/A
Controls:
Vehicle: 0.5% aqueous methylcellulose
Negative control: Vehicle
Positive control:Dimethylnitrosamine (DMN)
Comments:
Exposure conditions: N/A
Incubation and sampling times: N/A
Doses used in definitive study: 200, 500, 1000, and 2000mg sertaconazole nitrate/kg

Study design: Groups of 8 weeks old male rats (3/dose/time point) received gavage doses of test article in a constant volume of 10mL vehicle. The positive control DMN was administered intraperitoneally at 10, and 15mg/kg dose levels. Approximately between 2-4 and 15-16 post-dose hours, cells were isolated by *in situ* perfusion of livers. The cell viability ranged from 52 to 90%. The cell pellets obtained by

centrifugation of cell suspension were used to inoculate culture dishes ($0.5x10^6$ viable cells/dish). After attachment to cover slips (for 2 hours), the cultures were labeled with 10μCi/mL ^{3}H-thymidine for 4 hours. The cultures were prepared for analysis of nuclear labeling 18 hours after wash out of free radioactivity and addition of 0.2mM thymidine. The treated cells were then subjected to autoradiography by storing slides for 10 days in the light tight-boxes.

The UDS was measured from the net nuclear count, which was determined by counting the nuclear grains and subtracting from it the average number of grains in 3 nuclear-sized areas adjacent to each nucleus (cytoplasmic count).

Analysis:

No.of replicates: Three of the 4 replicate cultures/animal were used for UDS assay.
Counting method: Microscopic (1500x magnification)

Criteria for positive results: Compared to the vehicle control, at least 5 grain, and or 10% increase in the mean net nuclear grain count in the drug treated nuclei.

Summary of individual study findings:

Study validity: A clear-cut positive response was observed in-group treated with DMN. In addition, the values obtained for the negative control (vehicle) were within the criteria of assay acceptance (Table).

	UDS at 2-4 hour time point			UDS at 15-16 hour time point		
Group/ Mg/kg	Mean net nuclear grain count	%Cells with >5 mean net nuclear grains	Mean cytoplasmic grain count	Mean net nuclear grain count	%Cells with >5 mean net nuclear grains	Mean cytoplas-mic grain count
Vehicle	-2.2	1.8	9.7	-1.9	0.7	9.1
DMN 15mg	17.1	97.6	11.2	12.2	93.3	6.6
SN 2000[a]	-2.5	3.0	12.0	-2.2	3.6	12.4
SN 1000	-1.9	2.8	10.5	-1.6	1.3	8.9
SN 500	-1.7	3.8	10.7	-1.5	3.2	11.8

[a] Sertaconazole nitrate mg/kg

Study outcome: At both time points, the values for drug treated groups were similar to the vehicle control. Although the test article was evaluated at the highest appropriate dose level, none of the sertaconazole nitrate treated groups at any time point contained at least 5 mean net nuclear grain count, or at least 10% nuclei containing five or more grains. In contrast the values for positive control far exceeded the criteria set for a positive response. No dose or drug related trend was observed in the drug treated groups.

Under the assay conditions, the sertaconazole nitrate was evaluated as inactive in inducing UDS in the rat hepatocytes.

Genetic toxicology summary and conclusions: In a battery of *in vitro* and *in vivo* assays, sertaconazole nitrate did not exhibit any genotoxicity. In Ames *Salmonella typhimurium* assay (0.15 to15μg), no significant increase in the mean number of revertant colonies was observed in any of the test strains (TA-98; TA100; TA-102; TA-1535; TA-1537). In the mice micronucleus test (500-1000mg/kg), no statistically significant increase in the number of micronucleated polychromatic erythrocytes in the individual test groups or in the combined male and female data, was observed. In cells isolated from the drug treated mice, sertaconazole nitrate did not induce any unscheduled DNA synthesis. In an *in vivo* mice test (4000, 4500, and 5000mg/kg to mice), drug did not induce any sister chromatid exchange.

Labeling recommendations: The genotoxicity profile of sertaconazole nitrate is complete for labeling purpose.

VI. CARCINOGENICITY: No studies were conducted.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

4. Study title: Study of the effects on pre- and postnatal development, including maternal function in rats treated with sertaconazole nitrate via oral gavage administration

Key study findings: Modest effects of sertaconazole nitrate on a few reproductive and developmental indices were observed at the mid- and high-dose levels. NOEL was established at the low dose of 40mg sertaconazole nitrate/kg/day.

Study no.: 96-4096
Volume #, and page #: 15, and 5-10-1
Conducting laboratory and location:

Date of study initiation: 20 June 1997
GLP compliance: Yes
QA reports: Yes
Drug, lot #, radiolabel, and % purity: Lot# C-1003, purity 100%
Formulation/vehicle: 0.5% (w/v) aqueous methylcellulose suspension

Methods:

Species/strain: Rat/CD [Crl: CD Br]
Doses employed: 0, 40, 80, and 160mg/kg/day
Route of administration: oral

Study design: Approximately 9 weeks old time mated females received gavage doses of drug or vehicle from gestation day 6 through lactation day 20. The day of delivery was considered as lactation day 0.
Number/sex/group: 25 females/dose group

Parameters and endpoints evaluated:

Mortality and clinical observations (F_0 females): Routine examination twice daily, detailed physical examination on days 3, 6-22 gestation days, and lactation days 0-21. The signs of parturition were checked twice daily, and any evidence for difficult or prolonged parturition was recorded.

After the delivery, litters were evaluated for number of dead and alive pups and abnormalities. All live pups were separated by sex.

Body weights: Determined on gestation days 3, 6, 9, 12, 15, 18, and 20, and on lactation days 0, 4, 7, 10, 18, and 21. All F_1 pups were weighed on lactation days 0, 4, 7, 14, and 21; pups were also weighed on postnatal days 28, 35, and 42.

Food consumption: Gestation days 3, 6, 9, 12, 15 and 18, and lactation days 0, 4, 7, and 10.

Selection of F_1 rats: At least one pup/sex/litter (F_1 generation) was selected between lactation days 21-25 to provide a minimum number of 25/sex to investigate reproductive performance and behavior.

Behavioral evalaution of F_1 generation: In the pre-weaning period, animals were subjected to a battery of tests to evaluate their neurological development (auditory startle response, visual placing). In the postweaning period, rats were tested for motor activity, auditory startle habituation, learning and memory.

Reproductive assessment of F_1 generation: Approximately 90 days old pups (25/sex) were selected for mating. Each male was cohabited with the same female until mating was confirmed, or for 14 consecutive days. The brother-sister mating was avoided. On gestation day 20, the evidence for prolonged labor (if any) was recorded.

F_2 Generation: Litters were examined right after the delivery for any abnormalities, and for dead pups. The number of pups in each litter was recorded. On lactation days 0, 4, 7, 14, and 21, each pup was subjected to a gross physical examination, weighed and separated into sexes.

Necropsy:

F_0 Dams: Gross macroscopic examinations were conducted on all rats including those sacrificed on lactation day 21, found moribund or dead. The examination also included a count of uterine implantation scars.

F_1 Pups: Pups not selected for reproductive or behavioral assessments were sacrificed on day 21 of lactation. The F_1 males used in the reproductive component were sacrificed immediately after the last F_2 litter was delivered. F_1 rats used for behavioral assessment were sacrificed after all the tests were conducted.

F_2 Pups: These pups sacrificed on weaning were subjected to complete necropsy examination.

Results:

Mortality:

F_0 females:

One mid- and two high-dose females died during the study period. Mid-dose dam died after delivering 7 pups; four fetuses were found *in utero*. The first high-dose female died on gestation day 23; necropsy revealed 14 fetuses *in utero*. Second female was sacrificed moribund during the delivery. The macroscopic examination could not establish the cause of any of these deaths.

Clinical signs: Detailed physical examination during the gestation and lactation period did not reveal any drug-related signs of toxicity in F_0 females.

Body weight: During the gestation period, the gain in body weight was similar in all the F_0 groups. Between lactation days 1-21, the increased gain (28% at $p<0.01$) in body weight only in the mid-dose females was not considered drug related.

Food consumption: In the mid- and high-dose F_0 females, statistically significant decrease in food consumption was recorded between gestation days 6-18, however, these decreases were not associated with any changes in the body weights.

Toxicokinetics: N/A

In-life observations:

Dams: Sertaconazole nitrate at the high dose level affected several indices (Table).

F_0 females: Summary of delivery and litter data

Index Group(Mg/kg/day)	0.0	40	80	160
Pregnancy rate (%)	96	100	100	100
Females completing delivery (%)	100	100	96	88
With stillborn pups (%)	8	4	29	41**
Duration of gestation (Days)	22	22	22	22
Live birth (%)	100	100	96	93
Stillborn (%)	0.7	0.3	4.3*	7.1**
Pups dying/missing/or cannibalized (%) Days 5-21 Days 0-21	 0.7 1.0	 0.3 1.3	 0.0 1.4	 6.4** 7.6**
Pups surviving 21 days (%Lactation index)	99	100	100	91**
Live pups/litter Day 0 Day 21	 13 8	 12 8	 12 8	 11** 7

* $p<0.05$ ** $p<0.01$

Thus, the number of dead pups at birth was higher, and the live birth index was reduced. Two females delivered litters with only dead pups, together a total of 18 pups. The number of pups found moribund, missing, or cannibalized was significantly higher, and the number of live pups at birth was slightly but significantly lower.

At the mid-dose level, a significant increase in stillborn pups was observed. All low-dose data was comparable with the control.

The drug did not affect the pregnancy rate or sex ratio of pups.

Offspring:

F_1 generation: No deaths occurred in the drug treated pups. The actual cause of death for one control female died during week 10 could not be established. No clinical signs of toxicity were observed in the F_1 rats through lactation and postnatal period.

At birth, the mean body weights of pups at the mid- and high-dose groups were significantly greater (7-8% at $p<0.01$). However, the body weights were comparable with controls during remainder of the lactation period. On the other hand, the mean body weights of mid-dose male and female pups on lactation day 21 were reduced between 7-8% ($p<0.05$) A similar pattern was observed in both the sexes on postnatal days 28, 35, and 42. Since no such changes occurred in the high-dose pups, the change at the mid-dose level was not considered toxicologically important.

Sertaconazole nitrate did not affect the vaginal patency and preputial separation. One stillborn high-dose female pup exhibited the following malformations: microganthia, facial cleft, cleft palate, aglossia, and absence of external nares. Since no malformations were recorded in other pups, this single incident was considered spontaneous, and not toxicologically important. No treatment related malformations were observed in pups sacrificed at weaning. The behavioral assessment in the pre-weaning period did not reveal any abnormalities. In the post- weaning period, functional observational battery tests indicated no inter-group differences in motor activity, auditory startle habituation response, learning and memory.

The values of cohabitation data such as male and female mating and fertility indices, gestation length etc were similar in all the groups. Similarly, no drug or dose effect on the litter size, pup survival and sex distribution indices, number of live and stillborn pups was observed.

F_2 generation: No treatment related deaths occurred in pups sacrificed at weaning. Body weights at birth and throughout the lactation period were comparable in all the groups.

Terminal and necroscopic evaluations:

Dams: At the postmortem examination F_0 females did not reveal any drug related gross lesions.

Offspring: In the reproductive assessment group, five males died or were sacrificed moribund.

Group	Week of study	Clinical observations/Postmortem findings
Control	16	Distended abdomen and small intestine, emaciated
Low-dose	12	Emaciated, distended abdomen, hypothermic, a mass on left kidney, a muscle abscess on the right knee joint
Mid-dose	7	Autolysis noted at necropsy
	18	Lacrimation, malocculded incisors, red lung lobes
High-dose	8	No remarkable findings at necropsy

Since no deaths occurred in females, and no such clinical signs of toxicity were found in either of the sexes at necropsy, none of the male deaths were considered drug or dose related.

The postmortem examination of F_2 pups sacrificed at weaning did not reveal any drug related macroscopic lesions.

Summary of individual study findings: The drug related changes in mid- and high-dose F_0 females included a significant reduction in live birth indices, and a significant increase in the number of stillborn pups. No clear-cut statistically significant drug related effects were observed in F_1 litter data (F_2 pups). The low-dose (40mg/kg/day) was established as NOEL.

5. Study title: Study of the fertility and early embryonic development to implantation in the rat with sertaconazole nitrate via oral administration.

Key study findings: Sertaconazole nitrate did not affect fertility, implantation and embryonic development.

Study no.: 96-4095
Volume #, and page #: 13, and 5-8-2
Conducting laboratory and location:
Date of study initiation: March 27, 1997
GLP compliance: Yes
QA reports: Yes
Drug, lot #, radiolabel, and % purity: Lot # C-1003/100% purity
Formulation/vehicle: Sertaconazole nitrate in 0.5% (w/v) aqueous methylcellulose suspension

Methods:

Species/strain: Albino rats/CD [Crl:(SD) BR]
Doses employed: 0, 40, 80, and 160mg/kg/day
Route of administration: Oral

Study design: Approximately 9 weeks old male and 10 weeks old female rats were used in this study. Prior to mating, males received oral doses of drug or vehicle for 4 weeks and females for two weeks. Treatment continued during the mating and postmating periods in males and through gestation day 7 in the mated females. For mating, one male and one female from the same treatment group were cohabited. Cohabitation continued until signs of mating were observed, or for 14 consecutive days.
Number/sex/group: 24/sex/dose group.

Parameters and endpoints evaluated:

Mortality and clinical observations: rats were checked twice each day for mortality, and twice per week examinations were conducted to check for any clinical signs of toxicity.
Body weight: Pretest, day of study initiation, and twice weekly at 3 to 4-days intervals. Females were also weighed on gestation days 0, 3, 7, 10, and 15.
Food consumption: Twice per week, the consumption was also recorded in females on gestation days 0, 3, 7, 10, and 15.
Toxicokinetics: No investigations were conducted.
Estrus cycle: The estrous cycling was checked in females one week prior to the initiation of mating period, and daily during the mating period until the mating was confirmed. The estrus cycle was identified as one or more consecutive days with the vaginal smear. An interval in estrus was identified when there was a gap of at least one-day between the cycles.
Necropsy: Females were sacrificed on gestation day 15; after that the males were sacrificed. All animals were subjected to gross pathologic examination. In females, ovaries and uteri were removed to examine the number of corpora lutea, live, dead, or resorbed fetus. In males, testes and epididymides were weighed. The left epididymides from each male was processed for a count of caudal sperm and evaluation of sperm morphology; the sperms from the left vas deference were evaluated for motility.

Results:

Mortality: One mid-dose male died in week 8 of postmating period, the gross pathologic examination could not establish the cause of death. No other deaths occurred.
Clinical signs: No drug or vehicle related signs of toxicity were observed.
Body weight: In the pre-mating period (days 5-29), the body weight in the high dose males was significantly increased (14-24% at $p<-05$ to 0.01), however, no time related trend was observed. In no other period, any inter-group differences in body weight were recorded in either of the sexes.

Food consumption: There was a slight but statistically significant increase (4-8% at $p<0.05$) in the high-dose pre-mating males between days 5 to 26. No such changes were observed in either of the sexes at any other time period.
Toxicokinetics: N/A

In-life observations: Over eight-day period, 12-17% of females experienced one, 62-75% experienced two, and 8-25% females experienced three estrus intervals. No inter-group differences in the length of estrus cycle were observed.

The mating indices and pregnancy rates were not affected by the drug treatment. The mean number of days to mating for the control, low- mid- and high-dose groups was 2.4, 3.3, 2.2, and 2.4 days, respectively. The pregnancy rates for these groups were 96, 96, 100, and 96%. Similarly, no adverse effects of drug on the male mating performance or fertility were observed.

Terminal and necroscopic evaluations: The absolute and relative to body weights of testes and epididymis were not affected by the drug treatment. Sertaconazole nitrate also did not alter the count, morphology, and motility of sperms.

The uterine implantation data did not reveal any significant drug related changes (Table). No inter-group differences in the mean number of corpora lutea, uterine implantation sites, live fetuses, and resorptions were observed. The preimplantation losses in the low- and mid-dose groups were significantly lower than controls; however, because of absence of any such changes at the highest dose level, the incidence was not considered drug related.

Summary of cesarean data:

Index (Mean/animal) **Group**(Mg/kg/day):	0.0	40.0	80.0	160.0
Corpora lutea	16.7	16.7	15.5	15.9
Implantation sites	14.5	15.9	14.8	14.5
Preimplantation loss	2.2	0.8*	0.7*	1.3
Live fetuses	13.8	14.9	13.9	14.0
Postimplantation loss	0.7	1.0	0.9	0.6

*$p<0.05$

Summary of individual study findings: Sertaconazole nitrate had no effect on fertility, implantation, and early embryonic development. For reproductive toxicity, the 160mg/kg/day was established as NOEL

Reproductive and developmental toxicology summary and conclusions: All studies were conducted at the same dose levels (40, 80, and 160mg sertaconazole nitrate/kg/day) using the same (oral) route. In the rat teratogenicity study, drug had no effect on the implantation; the minor insignificant intra- and inter-group differences in the post-implantation losses were considered to be incidental. The number of live fetuses per litter, fetal sex ratio and body weights in all drug groups were comparable to the controls. In the high-dose group, one fetus exhibited a skeletal malformation (absent sternebra), while one dead fetus on external examination indicated omphalocele. These abnormalities were considered to be insignificant and incidental.

In the rabbit teratogenicity study, sertaconazole nitrate did not affect the implantation or post-implantation losses. The mean number of fetuses per litter, fetal weight, and sex ratios were similar in all groups. In the high-dose group, two fetuses from two litters showed arthrogryposis

or acaudia. A 1.6% incidence for these external malformations was well within the range of historical control data provided by the sponsor (acaudia=1.6-20%, arthrogryposis=3.3-20%). Nine fetuses from four litters had malformations of ribs and the vertebral column. These malformations also occurred within the range of historical control data (7% in high-dose versus 0-15% in historical controls). Also none of these incidences were statistically significant.

It was inferred that sertaconazole did not produce any maternal toxicity, embryotoxicity, or teratogenicity in rats and rabbits.

In the rat pre- and postnatal development study, the drug related changes in mid- and high-dose F_0 femlaes included a statistically insignificant reduction in live births at the mid- (4%) and high-dose (7%) levels. An increase in the number of stillborn pups observed at the mid- (21%, non-significant) and high-dose (33% at $p<0.01$) occurred at 121-242 times the maximum recommended human dose (20-40 times in terms of surface area). No clear-cut statistically significant drug related effects were observed in F_1 litter (F_2 pups) data. The low-dose (40mg/kg/day) was established as NOEL for pre- and post-natal development.

In the rat segment I study, sertaconazole nitrate had no effect on fertility, implantation to early embryonic development. The NOEL for reproductive toxicity was considered to be 160mg/kg/day.

Labeling recommendations: The reproductive and developmental toxicology profile for labeling purpose is complete.

VIII. SPECIAL TOXICOLOGY STUDIES:

6. Study title: Autoradiographic study on the whole animal after the dermal administration of sertaconazole ^{14}C nitrate 2% cream to the mouse.

Key study findings: Only a small amount of sertaconazole nitrate is topically absorbed.

Study no: B-352/96
Volume #, and page #: 17, 5-12-162
Conducting laboratory and location: Research Centre Ferrer Group, Barcelona, Spain
Date of study initiation: June 1996
GLP compliance: No
QA reports: No:
Drug, lot #, radiolabel, and % purity: Lot # not provided /**Sertaconazole ^{14}C nitrate** (specific activity 109 μCi/mg), % purity not provided
Formulation/vehicle: Sertaconazole nitrate Cream, 2%, in vehicle containing [redacted] Sorbic acid [redacted] and water [redacted]

Methods:
Dosing: 10mg sertaconazole nitrate/kg containing 10μCi of labeled drug in volume of 10μL.

Observations and times:

Four male Swiss nude mice (20g) fasted overnight received a single dermal application of drug formulation covering a surface area of 2x2cm on the back. Animals were sacrificed at the following post-application hours: one at 0.5, two after 2.5 hours, fourth after 24 hours. Anaesthetized animals frozen in liquid nitrogen were cut into sections of 20 µm. The serial sections were fixed to autoradiographic plates and kept in cassette for 12 days to develop.

Results: At 0.5 hour, most of the administered radioactivity was found on the application site. In addition to the application site, at 2.5 hours, the traces of radioactivity were also found in the liver, kidney, lungs, and stomach wall. After 24 hours, in addition to these organs, traces of radioactivity were also present in the excretory organs such as gall bladder, and in the intestinal content.

Summary of individual study findings Conclusions: The data indicated very little systemic absorption of drug via the dermal route.

7. Study title: Autoradiographic study on the whole animal after oral administration of sertaconazole ^{14}C nitrate to the mouse.

Key study findings: Results indicated a rapid metabolism and excretion of drug.

Study no: B-339/96
Volume #, and page #: 17 and 5-12-179
Conducting laboratory and location: Research Centre Ferrer Group, Barcelona, Spain
Date of study initiation: June 1996
GLP compliance: No
QA reports: No
Drug, lot #, radiolabel, and % purity: Sertaconazole nitrate; % purity not provided; Specific activity 109µCi/mg
Formulation/vehicle: 2.5% Solution/Arlantone/sodium bisulphite/nipagain/acetic acid/NaOH/ water

Methods: Four male nude Swiss mice (20g) fasted overnight received gavage dose of the test solution. One animal was killed after 10 minutes, two after 2.5 hours, the last after 24 hours post-dose. Rest of the procedure was similar to dermal autoradiogrphy study.

Dosing: 0.2mL/animal (1.5µCi/animal; 10mg sertaconazole nitrate/kg)

Observations and times: A large amount of the administered radioactivity was found in the GI-tract followed by liver; the small amounts of drug were also found in the kidney and tissues with high fat content.

Results: The data indicated a fast tissue distribution of radioactivity, with major amounts found in the liver and intestinal content at 2.5 hours pot-dose. At 24 hours, the amounts were much lower, indicating a little chance of accumulation of sertaconazole and or its metabolites.

Summary of individual study findings: Data indicated rapid metabolism and elimination of drug and or its metabolites.

8. Study title: Autoradiographic study on the whole animal after the subcutaneous administration of sertaconazole ^{14}C nitrate to the mouse.

Key study findings: A rapid metabolism and elimination were indicated.

Study no: B-353/96
Volume #, and page #: 17, and 5-12-195
Conducting laboratory and location: Research Centre Ferrer Group, Barcelona, Spain
Date of study initiation: June 1996
GLP compliance: No
QA reports: No
Drug, lot #, radiolabel, and % purity: Same as in dermal study above.
Formulation/vehicle: 2.5g sertaconazole nitrate in vehicle containing

and water

Methods: Three male nude Swiss mice (20g) fasted overnight received a single subcutaneous injection of the test solution.
Dosing: 0.2mL of 10mg sertaconazole nitrate/kg containing 0.3μCi of the labeled drug/animal

Observations and times: First animal was sacrificed at 30 minutes, second at 2.5 hours, and last at 24 hours post-dose. The procedure for autoradiography was similar to dermal study above.

Results: At 2.5 hours post-dose, radioactivity was distributed in decreasing order of amount to gallbladder, liver, kidney, stomach and in the intestinal content. Much lower amounts were found in the tissues with high lipid content and lungs.

Summary of individual study findings: Data indicated rapid subcutaneous absorption, metabolism and excretion of drug.

Conclusions: Using three different routes of administration and the autoradiographic technique, the tissue distribution of drug radioactivity was examined at three different post-dose time points. The data indicated that at 10-30 minutes, irrespective of the route, no systemic radioactivity was detected. The maximum amount by all routes was detected at 2.5 post-dose hours. The major amount of radioactivity was found in the liver, gallbladder and intestinal content, and smaller amounts were present in kidney and lungs. At 24 hours, the level of radioactivity in all organs was much reduced, indicating a rapid elimination of drug and or its metabolites. In the dermal study, most of the drug remained on the site of application, and only very small fraction was systemically absorbed. Data of all studies indicated that irrespective of the route of administration, the chances of any significant accumulation of drug in the body are negligible.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: The efficacy and safety of sertaconazole nitrate were evaluated in a number of *in vivo* and *in vitro* studies. In experimental *trichophytosis* in guinea pigs, topical applications of 2% Sertaconazolre nitrate cream reduced the size of lesions and alopecia, and in a reasonably short period eradicated the organism from the infected sites. In a rat ear irritation assay, sertaconazole exhibited significant anti-inflammatory activity. In a set of pharmacodynamic studies, oral (up to 100mg/kg) and intravenous (up to 5mg/kg) doses did not induce any functional changes in the cardiovascular and respiratory systems in mice. However, a slight change in the behavior of mice (motor incordination, increased defecation) at higher oral (1g/kg) and intraperitoneal (300mg/kg) dose level was observed.

Data from a dozen of single and multidose, multispecies, and multiroute pharmacokinetic studies revealed that the topical absorption of sertaconazole from 2% Sertaconazole nitrate Cream never exceeded 18% of the administered dose. Following topical applications, very low amounts of drug and its active metabolites (as measured by a microbiological assay) were found in the plasma, liver, and kidney, indicating a rapid hepatic metabolism. This assumption was also supported by multi route (oral, dermal and subcutaneous) autoradioagraphic studies in mice. The maximum amount of radioactivity by all routes was detected at 2.5 post-dose hours, and most of it was found in the liver, gallbladder and intestinal content with smaller amounts present in kidney and lungs. At 24 hours, the concentration of radioactivity in all organs was much diminished, indicating a rapid elimination of drug and or its metabolites. These data suggested that the drug metabolism was rapid with very little chance of accumulation, and the major portion of it was excreted through the bile. The low oral bioavailability of 48% in rats also confirmed a rapid metabolism. The half-life of sertaconazole in the rat was about 5.4 hours, and it was still shorter in the rabbit. In a nutshell, the pharmacokinetic profile of sertaconazole has revealed a limited dermal absorption, insignificant tissue accumulation, and fast metabolism and elimination. However, it must be mentioned that no attempts were ever made to characterize the metabolites of sertaconazole.

In comparison, only 0.5% of the [^{14}C]-Sertaconazole nitrate Cream applied to normal and stratified skin of healthy male human volunteers was absorbed. Furthermore, after multiple topical applications of increasing doses of 2% cream formulation, or administration of a single 500mg-sertaconazole nitrate vaginal tablet, the plasma drug levels in humans were still below the detection limit.

The acute, subchronic, and chronic toxicity studies conducted at fairly appropriate dose levels in several species did not reveal any significant irreversible long-term adverse effects. In a 3-month dermal studies in rats and dogs (10, 20, and 40mg/kg/day) conducted with 2% cream formulation, the NOEL for systemic toxicity was considered to be greater than 40mg/kg/day. In six-month oral studies in rats (15, 60, and 240mg/kg/day) and dogs (7, 30, and 120mg/kg/day), sertaconazole was well tolerated.

In a rabbit assay, sertaconazole nitrate was slightly irritating. However, no clear picture emerged from the sensitization assay in guinea pigs, since both the placebo and sertaconazole cream not only produced irritation (compared to their corresponding water controls) but also caused a mild

sensitization reaction following the challenge dose. Therefore, under the assay conditions, both sertaconazole nitrate cream and its placebo cream caused mild irritation and sensitization. According to the sponsor, in clinical trials, sertaconazole nitrate cream exhibited little potential to induce contact dermal photoallergy or contact dermal sensitization.

In a battery of assays, sertaconazole nitrate did not exhibit any genotoxicity. In Ames bacterial test, none of the test strains produced any significant increase in the number of the revertant colonies. In mice micronucleus assay, no increase in the polychromatic erythrocytes was observed in either of the sexes. In hepatocytes isolated from drug treated mice, sertaconazole did not induce any unscheduled DNA synthesis. Drug also did not induce any sister chromatid exchange in a mice assay.

All reproductive and developmental toxicity studies were conducted using oral doses of 40, 80, and 160mg/kg/day. In two teratogenicity studies in rats and rabbits, sertaconazole nitrate did not cause any maternal toxicity, embryotoxicity, or teratogenicity. It must be pointed out that a dose 230 greater in terms of body weight (40-80 times in terms of surface area) than the maximum recommended human dose failed to cause any maternal toxicity. In fact, if actual amount of absorption (0.5%) in humans is taken into account, the margin of safety will be in four digits. The highest dose was considered to be the NOEL. In the rat pre- and postnatal development study, drug-related effects such as reduction in live birth indices, and an increase in the number of stillborn pups, were observed at the mid- and high-dose levels. The low-dose was considered a NOEL. In rat segment I study, sertaconazole nitrate did not exhibit any effect on fertility, implantation to early embryonic development. The NOEL was considered to be the high-dose.

Taking into account the pharmacokinetic, toxicologic, genotoxic, and epidemiologic profiles of sertaconazole nitrate, chemical carcinogenicity studies are not warranted. First, sertaconazole did not exhibit any genotoxicity potential in a battery of *in vitro* and *in vivo* assays. Second, it is structurally similar to several others imidazole derivatives where no experimental evidence of carcinogenicity have been observed. Third, the compound is biodisposed very rapidly, and hardly any parent drug and or its metabolites are retained in the tissues. The median retention time for sertaconazole in animals is low (~3.8 hours). Fourth, the dermal absorption in humans was much lower than in the animals. In fact, after the dermal applications in humans, drug was not even detectable in the plasma. Therefore, in all probability, the pharmacokinetic behavior of sertaconazole will not permit a threshold level required for nongenotoxic injuries (e.g. peroxisome proliferation).

In human testing, the drug product did not cause any phototoxicity. In the second clinical study, formulation exhibited little potential to induce contact dermal photoallergy or contact dermal sensitization. The photostability of Sertaconazole nitrate Cream 2% tested according to ICH guideline (Guidance for Industry, *Q1B Photostability Testing of New Drug Substances and Products, November 1996*) indicated that the drug substance was resistant to photodegradation. Finally, Sertaconazole nitrate cream formulation has been marketed in several countries for many years, and to date no serious adverse effects or proliferative dermal lesions raising health concerns have been reported. Looking into all these facts, a photocarcinogenicity study is not warranted.

In rat and rabbit oral teratogenicity studies, and an oral reproductive toxicity study in rats, a NOEL of 160mg/kg/day was established. It provided 230 times the margin of safety in terms of body weight, and 40 to 80 times in terms of body surface area. The NOEL of 40mg/kg/day in oral pre- and post-natal development study in rats will provide margin of safety of 61 times in terms of body weight, and 10 times in terms of body surface area. However, it must be mentioned that these calculations are based on the assumptions of a maximum use of 2grams cream formulation per day and 100% systemic absorption. However, in the dermal pharmacokinetic studies, the systemic absorption never exceeded 18%. Therefore, in real terms, the margin of clinical safety will be much greater.

General Toxicology Issues: None

Recommendations: From non-clinical point of view, I have no objection to the approval of this new drug application.

Labeling with basis for findings:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term studies to evaluate the carcinogenic potential of Sertaconazole nitrate have not been conducted.

Pregnancy

Teratogenic effects: pregnancy category

Reviewer signature: _____

Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(See memo attached)

cc: list:

X. APPENDIX/ATTACHMENTS:

Addendum to review:

Other relevant materials (appended consults, etc.):

Any compliance issues:

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

/s/

Kumar Mainigi
5/2/02 02:23:51 PM
PHARMACOLOGIST

Abby Jacobs
5/3/02 06:57:15 AM
PHARMACOLOGIST
Please see my supervisory pharmacologist memo
Please see my supervisory pharmacologist memo

Jonathan Wilkin
5/17/02 12:07:10 PM
MEDICAL OFFICER
See Supervisory Pharm/Tox memo

Supervisory Pharmacologist's memo on NDA 21-385 sertaconazole cream 2% 5/3/02 N21385sertb.doc
A. Jacobs

I concur that there are no pharm/tox reasons why sertaconazole should not be approved. I differ from the primary reviewer in aspects of the summary of nonclinical findings, conclusions and recommendations, recommendations for the pregnancy category, the need for phase 4 dermal carcinogenicity studies, why photococarcinogenicity studies are not needed, and other labeling issues. See my labeling suggestions at the end of this memo.

1. I think that the pregnancy category should be C: [redacted] The peri-postnatal study finding of a significant reduction in live birth indices and a significant increase in the number of stillborn pups is described in the labeling, as is current CDER practice. Nefazodone has an analogous label; there were no malformations but there were peri-postnatal effects. The category for such fetotoxicity is C. Since no maternal toxicity was seen in either the rat or rabbit developmental toxicology studies, these studies would not be considered adequate for an oral indication for sertaconazole. This is another reason for the pregnancy category being category C. There is no need to repeat the developmental toxicology studies for the current indication/formulation.

2. It is not clear why so many external and skeletal variation/malformations are seen in control animals (external: three control fetuses from two litters with filamentous tail or kinked or reduced tail; skeletal: four control fetuses from three litters with rib and vertebral column malformations. The arthrogryposis or acaudia, seen in two litters from the highest dose group were not seen in controls. The primary reviewer reported in his original IND 50,726 review (and first two NDA 21-285 draft reviews) that four fetuses from two litters had these malformations and that these incidences were within the historical controls. The sponsor was asked to supply historical incidences of these two malformations, since the incidences appeared to exceed normally observed incidences. The sponsor did not have on hand the incidences of malformations broken down by individual type. Subsequently, I found in sponsor–supplied material in the NDA that arthrogryposis or acaudia were seen in two fetuses (not the four fetuses described by the primary reviewer) in two litters from the highest dose group. The primary reviewer changed the incidences to the lower numbers in draft #3 and these lower numbers are in the final version. Since the higher incidences were cited in the original review of IND 50,726, an addendum probably should be written to that IND review.

3. The entire [redacted] ection (after the [redacted] , should be deleted from the labeling. The material included by the sponsor in this section does not belong in labeling.

4. Since sertaconazole was only tested in Salmonella at up to 15 µg per plate, the assay would be considered inadequate for sertaconazole, and mention of the [redacted] should be removed from the labeling. Although adequate tests for clastogenicity were conducted, adequate tests of mutagenicity were not conducted. A mouse TK $^{+/-}$ lymphoma assay should be conducted for sertaconazole if it is submitted for a new indication.

5. I think that there should be a phase 4 commitment to conduct a [redacted] dermal carcinogenicity study if this product is expected to be used repeatedly for the proposed indication. This would be consistent with our division practice for this indication. (Per ICH S1A, "For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed."). The need for a dermal carcinogenicity study is guided by the chronic nature or rate of recurrence of the indication and not by systemic absorption of the drug substance or the absence of genotoxicity. Recently a dermal vehicle of a nongenotoxic drug substance applied only two times per week was found to cause skin neoplasms in mice. A cause for concern is not necessary to support the need for dermal carcinogenicity studies for the tinea pedis indication. The long-term effects of the entire formulation on the skin are of interest. Furthermore, the skin receives large doses of sertaconazole and its vehicle. Sertaconazole is reported to achieve high epidermal concentrations following cutaneous application. Cutaneous absorption was 64% of the dose at 12 hours and 72% at 24 hours following topical application of a 2% cream (Farre M, Ugena B, Badenas JM et al: Pharmacokinetics and tolerance of sertaconazole in man after repeated percutaneous administration. Arzneimittelforschung

1992; 42:752-754. Hyperplasia and hyperkeratosis were seen in the skin of dogs that received 2% sertaconazole cream or vehicle cream for 92 days. This further supports the need for a phase 4 dermal carcinogenicity study.

6. Our division practice has been to not ask for evaluation of photococarcinogenic potential for the tinea pedis indication. The need for such a study would be reevaluated if the indication for sertaconazole changed. The need for evaluation of photococarcinogenic potential is guided by the indication and extent of skin exposure to sun, not by photostability or phototoxicity of the drug substance (per division practice

7. Suggested labeling changes follow:

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies to evaluate the carcinogenic potential of sertaconazole nitrate ——— have not been conducted. No ——— clastogenic potential was observed in a mouse micronucleus test.

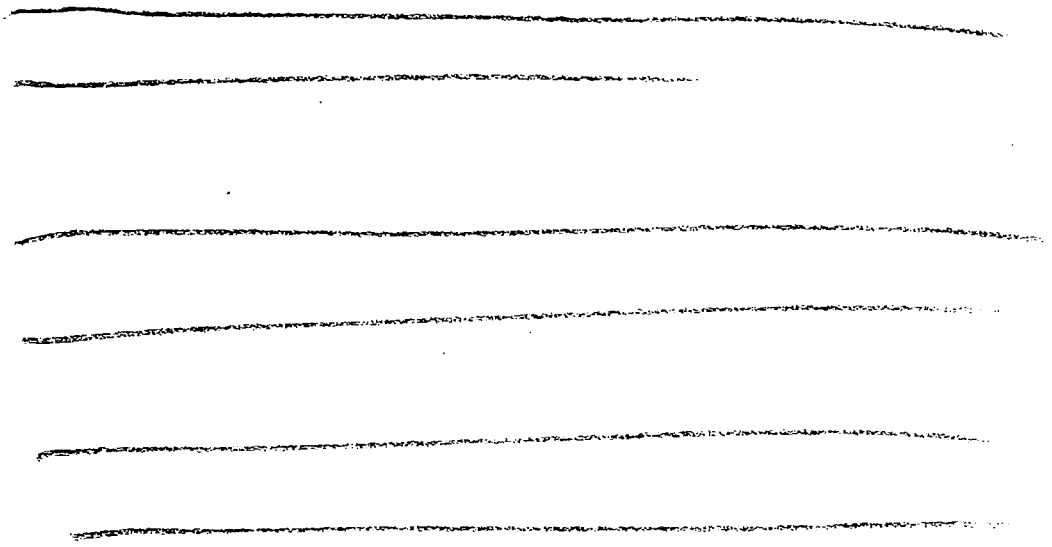
——. Sertaconazole nitrate was considered negative for sister chromatid exchange (SCE) in the *in vivo* mouse bone marrow SCE assay. There was no evidence that sertaconazole nitrate induced unscheduled DNA synthesis in rat primary hepatocyte cultures. Sertaconazole nitrate exhibited no toxicity or adverse effects on reproductive performance or fertility of male or female rats given up to ——— 60 mg/kg/day orally by gastric intubation (16 times the maximum recommended human dose on a body surface area comparison).

Pregnancy: ***Teratogenic Effects. Pregnancy Category B C:*** Oral reproduction studies in rats and rabbits did not produce any evidence of maternal toxicity, embryotoxicity or teratogenicity of sertaconazole at oral dose of ——— 160 mg/kg/day) — 40 times (rats) and 80 times (rabbits) the maximum recommended human dose on a body surface area comparison). In an oral peri-postnatal study in rats, a reduction in live birth indices and an increase in the number of still-born pups was seen at

80 and 160 mg/kg. There are no adequate and well-controlled studies that have been conducted on topically applied [redacted] cream, 2% in pregnant women. Because animal reproduction studies are not always predictive of human response, [redacted] cream, 2% should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known if sertaconazole nitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when prescribing [redacted] cream, 2% to a nursing woman.

Pediatric Use: The efficacy and safety of [redacted] cream, 2% have not been established in pediatric patients [redacted]



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

/s/

Abby Jacobs
5/3/02 07:21:02 AM
PHARMACOLOGIST
This is my supervisory pharmacologist memo with labeling and phase 4 recommendations
See my labeling and phase 4 recommendations

Jonathan Wilkin
5/17/02 12:10:54 PM
MEDICAL OFFICER

MEMORANDUM
July 22, 2002

SUBJECT: NDA 21-385 (Sertaconazole nitrate; ERTACZO Cream, 2%)
TO: File

I concur with the proposed product label as amended. In addition, I concur that results of a dermal carcinogenicity study should be provided in order to approve this marketing application.

Kenneth L. Hastings, Dr.P.H.
Acting Associate Director for Pharmacology/Toxicology
Office of Drug Evaluation V

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

/s/

Kenneth Hastings
7/22/02 04:18:53 PM
PHARMACOLOGIST