

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-946**

**PHARMACOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-946  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 09/28/05  
PRODUCT: TRADENAME Gel (Ketoconazole USP 2%)  
INTENDED CLINICAL POPULATION: patients with seborrheic dermatitis  
SPONSOR: Barrier Therapeutics Inc.  
DOCUMENTS REVIEWED: electronic submission  
REVIEW DIVISION: Division of Dermatology and Dental Drug  
Products (HFD-540)  
PHARM/TOX REVIEWER: Jill C Merrill  
PHARM/TOX SUPERVISOR: Paul C Brown  
DIVISION DIRECTOR: Dr. Stanka Kukick  
PROJECT MANAGER: Margo Owens

Date of review submission to Division File System (DFS):

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## ***EXECUTIVE SUMMARY***

### **I. Recommendations**

- A. **Recommendation on approvability – TRADENAME Gel for the treatment of seborrheic dermatitis is approvable from a pharmacological/toxicological perspective**
- B. **Recommendation for nonclinical studies – The sponsor has agreed to perform a phase 4 dermal carcinogenicity study, to be initiated as soon as the sponsor receives drug approval.**
- C. **Recommendations on labeling – Acceptable with modifications**

### **II. Summary of nonclinical findings**

1. Brief overview of nonclinical findings - The sponsor has conducted a 90-day dermal toxicity study in mice (10/sex/group) at doses of 0, 40, 80, 160, and 400 mg/kg. An additional set of 54 animals/sex/group were treated (40 to 400 mg/kg) for toxicokinetic analyses. Toxicokinetic analysis revealed that animals were systemically exposed to ketoconazole. However, no accumulation occurred and a dose response relationship in plasma drug concentrations was not observed on days 27 and 89. This phenomenon is likely due to oral ingestion subsequent to animal grooming as ketoconazole has been shown to be undetectable in rabbit plasma after dermal application. Dermal application of ketoconazole to the mouse for up to 17 days (400 mg/kg) or a minimum of 90 consecutive days (40, 80, and 160 mg/kg) did not produce mortality or clinical signs of toxicity. Irritation at the site of test article application was noted grossly at 160 and 400 mg/kg and microscopically at all dose levels examined (40, 80, and 160 mg/kg). In addition, pigmentation of the liver was observed at all dose levels and a higher incidence of renal hypertrophy was noted microscopically in the 80 and 160 mg/kg animals. Thyroid glands were also noted to be slightly heavier in all treated male groups (40, 80, and 160 mg/kg). However, microscopic examination of this organ did not reveal any notable structural changes so the biologic relevance of this change was unclear. Therefore, based on the above findings, a NOEL was not obtained for this study. Ketoconazole 2% gel was found to be a non-irritant when tested in rabbit eyes. When tested in the Ames assay, ketoconazole alone was found to be non-mutagenic to *Salmonella typhimurium* in the presence and absence of metabolic activation. A complete battery of genotoxicity studies of 2% ketoconazole were performed in combination with desonide. In an Ames assay, 2% ketoconazole and 0.05% desonide, the ketoconazole-desonide combination product, did not significantly increase the number of revertant colonies in the presence or absence of S9 metabolic activation, and the study was considered negative. An *in vitro* study evaluating the potential for 2.0% ketoconazole and 0.05% desonide gel to induce chromosomal aberrations in Chinese hamster ovary cells was also conducted.

Although there was no significant increase in chromosomal aberrations or polyploidy there was an increase in endoreduplication at 10/0.25 and 20/0.5 µg/mL ketoconazole/desonide with metabolic activation (8.5% and 11%, respectively). Additionally, cytotoxicity was insufficient (as per ICH genotoxicity guidelines S2A, section 2.1.2.2) and higher concentrations should have been analyzed. When tested in an *in vivo* mouse micronucleus study the ketoconazole and desonide combination was negative with the exception of one (of six) mouse with a clearly positive response at the high dose of the drug product at 48 hours. A second mouse micronucleus test for the ketoconazole/desonide combination was subsequently conducted and is considered negative.

2. Pharmacologic activity - Ketoconazole inhibits the conversion of lanosterol to ergosterol, by inhibiting 14 $\alpha$  demethylase via inhibition of cytochrome P450 enzymes. Ergosterol is the main sterol in the membranes of fungi and is necessary for fungal cell membrane integrity. By blocking the synthesis of ergosterol, ketoconazole causes cell membrane disruption and ultimately fungal cell death.
3. Nonclinical safety issues relevant to clinical use - none

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## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-946

Review number: 1

Sequence number/date/type of submission: 000/09-28-05/NDA submission

Information to sponsor: Yes (x) No ( )

Sponsor and/or agent: Barrier Therapeutics Inc.

Manufacturer for drug substance: DPT Laboratories, Ltd., San Antonio, TX 78215

Reviewer name: Jill C Merrill

Division name: Dermatology and Dental Drug Products

HFD #: 540

Review completion date: 05-01-06

#### Drug:

Trade name: TRADENAME Gel

Generic name: Ketoconazole USP 2% Topical Gel

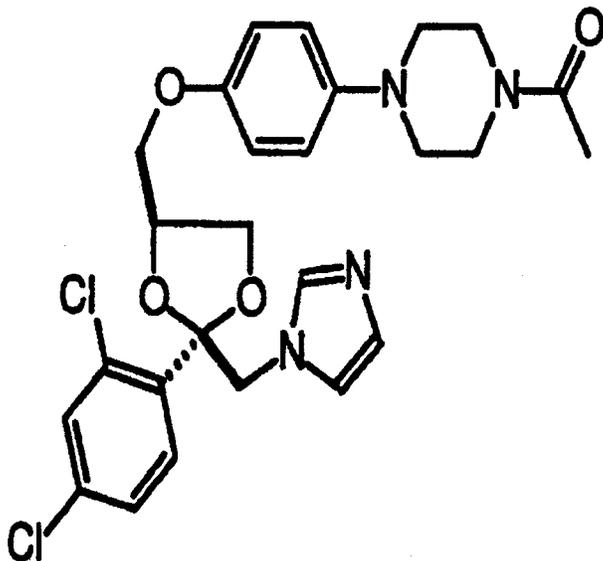
Code name: Formula # BTX-1

Chemical name: *cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine

CAS registry number: 65277-42-1

Molecular formula/molecular weight: C<sub>26</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub> / 531.48

Structure:



**Regulatory status:** This NDA was submitted under section 505(b)(1) of the FD&C Act. It was supported with pharmacology/toxicology information obtained from nonclinical studies performed by the sponsor and those for which they obtained the right-of-reference.

**Relevant INDs/NDAs/DMFs:**

IND 57, 462

IND \_\_\_\_\_

NDA 19-927, ketoconazole 2% shampoo (right to reference)

NDA 19-084, ketoconazole 2% cream

NDA 19-648

NDA 18-533, ketoconazole 200 mg tablets (right to reference)

DMF \_\_\_\_\_

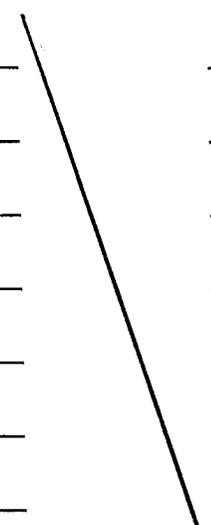
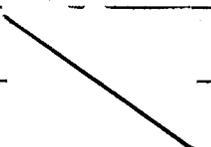
DMF \_\_\_\_\_

**Drug class:** Imidazole antifungal agent

**Intended clinical population:** seborrheic dermatitis

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**Clinical formulation: 2% gel**

Ingredient	Weight %	
Ketoconazole, USP	2.0%	
Polyethylene glycol 400		
Propylene glycol, USP		
Glycerin, USP		
PPG-15 Stearyl ether		
Hydroxypropyl cellulose		
Ascorbic acid, USP		
Butylated hydroxytoluene		
Citric acid monohydrate, USP		
Alcohol USP		34.0%
FD&C Yellow No. 6		
D&C Yellow No. 10		

**Route of administration:** topical

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Studies reviewed within this submission:**

Absorption of ketoconazole in the dog after repeated vaginal application and after application on the intact and abraded skin, R 41 400/41

Pharmacokinetics and metabolism of ketoconazole in animals, 41 400/35

The binding of R 41 400 to human plasma proteins and blood cells, and to subcellular fractions of rat liver, lung, kidney and small intestine, R 41 400/24

Ketoconazole (R 41 400) in the beagle dog: transition into the milk. Relation to plasma levels, R 41 400/32

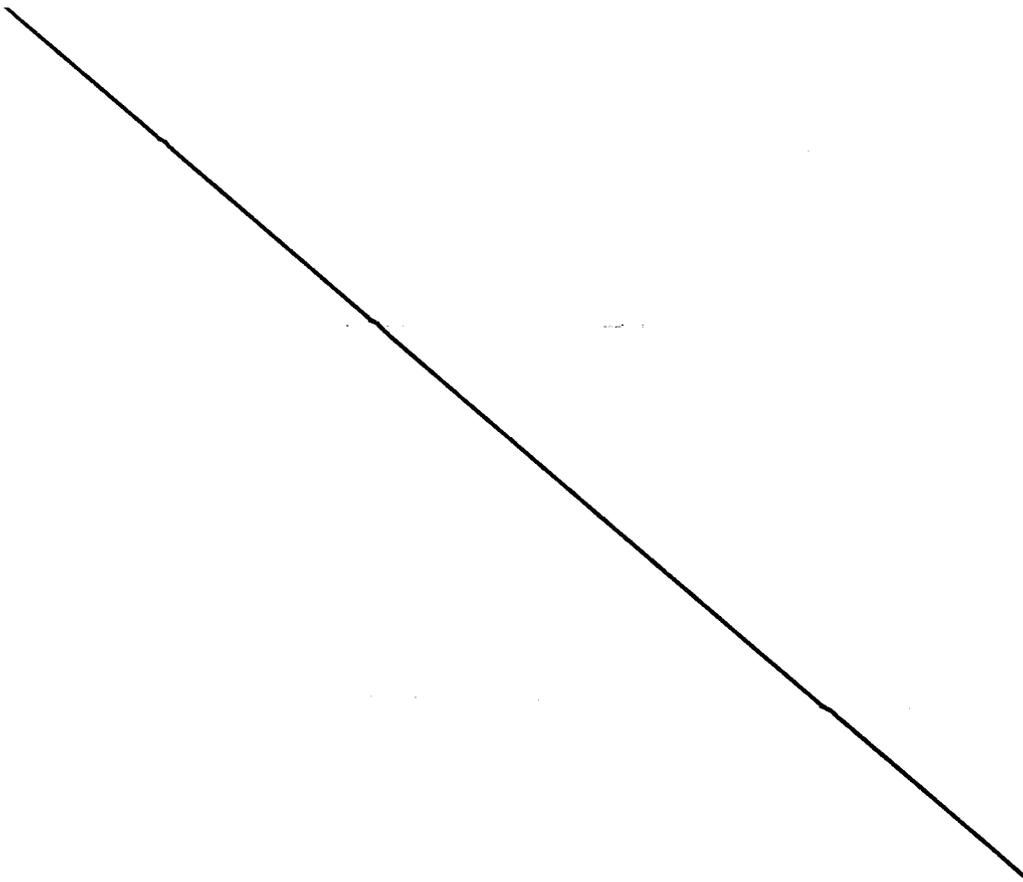
A comparison between the excretion and biotransformation of ketoconazole after oral administration in male and female rats, R 41 400/28

The excretion and biotransformation of \_\_\_\_\_ (R41400) in the adult beagle dog after oral administration of the \_\_\_\_\_

A primary eye irritation study in rabbits with ketoconazole USP 2% topical gel, MSW00017

Mutagenicity test on ketoconazole:desonide (40:1 ratio) in the *in vivo* mouse micronucleus assay, 98-017T

**Studies not reviewed within this submission:**



## 2.6.2 PHARMACOLOGY

### 2.6.2.1 Brief summary

A large number of studies have been conducted demonstrating the broad-spectrum anti-fungal activity of ketoconazole (Faergemann, 1984; Faergemann, 1988; Faergemann, 2000; Van Gerven and Odds, 1995; Van Cutsem *et al.*, 1987; Van Cutsem *et al.*, 1990). *Malassezia furfur*, a lipophilic yeast that is also known as *Pityrosporum ovale* or *Pityrosporum orbiculare* has been implicated as an important organism in the etiology of seborrheic dermatitis (Faergemann, 2000). Ketoconazole has been shown to be effective against:

*Malassezia furfur*, a yeast also known as *Pityrosporum ovale* or *Pityrosporum orbiculare*

*Trichophyton rubrum*

*Trichophyton mentagrophytes*

*Epidermophyton floccosum*

*Candida albicans* and *tropicalis*

### 2.6.2.2 Primary pharmacodynamics

**Mechanism of action:** The mechanism of action for ketoconazole's anti-fungal activity is related to the drug's induced changes on the plasma membrane and cell wall, which results in an elevation in cell volume (NDA 19-927). Ketoconazole inhibits the conversion of lanosterol to ergosterol, by inhibiting 14 $\alpha$  demethylase via inhibition of cytochrome P450 enzymes (Dismukes, 1988; Feldman, 1986; Borgers *et al.*, 1983; NDA 18-533; NDA 19-927). Ergosterol is the main sterol in the membranes of fungi and is necessary for fungal cell membrane integrity. By blocking the synthesis of ergosterol, ketoconazole causes cell membrane disruption and ultimately fungal cell death.

**Drug activity related to proposed indication:** Seborrheic dermatitis is an inflammatory scaling disease of the scalp, face, and other areas of the skin with sebaceous glands. It is thought to be related to fungal skin infections. Because ketoconazole blocks the

synthesis of ergosterol, a vital component of fungal cell membranes, it results in fungal cell death and as such is thought to be effective in the treatment of seborrheic dermatitis. Primary pharmacology studies indicated that topical ketoconazole was effective in the treatment of superficial fungal infections caused by *Malassezia furfur*. Similarly, oral ketoconazole was also effective against systemic *Malassezia furfur* infections.

### 2.6.2.3 Secondary pharmacodynamics

Secondary pharmacology studies demonstrated that topical ketoconazole treatment was effective in treating vaginal and superficial candidiasis caused by *Candida albicans* and dermatophytosis caused by *Microsporum canis* or *Trichophyton mantagrophytes*. In addition, the results of secondary pharmacology studies demonstrated that oral ketoconazole was effective in treating the following conditions:

Coccidioidomycosis (*Coccidioides immitis*)  
Cryptococcosis (*Cryptococcus neoformans*)  
Systemic candidiasis, superficial candidiasis, vaginal candidiasis (*Candida albicans*)  
Pulmonary blastomycosis (*Blastomyces dermatitidis*)  
Disseminated paracoccidiomycosis (*Paracoccidioides brasiliensis*)  
Disseminated trichophytosis (*Trichopyton mentagrophytes*)  
Histoplasmosis (*Histoplasma capsulatum*)

### 2.6.2.4 Safety pharmacology

A cardiovascular safety study was conducted in dogs during which ketoconazole was administered at an intravenous dose of 5 mg/L (NDA 18-533). In this study, ketoconazole produced some slight prolongation of the duration of action potential and the effective refractory time in the purkinje fibers and the papillary muscle. The recovery time of the purkinje fibers was slightly increased (NDA 18-533). There were no other treatment related effects noted. The cardiovascular safety of ketoconazole was investigated in anesthetized dogs following an intravenous dose of 5 mg/kg (NDA 18-533). In these animals ketoconazole treatment caused no cardiac or hemodynamic effects. When 7.37 mg/kg was administered intravenously followed by an intravenous bolus dose of 10 mg/kg, there were insignificant transient changes in cardiac or hemodynamic parameters up to 2.5 minutes postdose.

### 2.6.2.5 Pharmacodynamic drug interactions

The potential for ketoconazole to cause pharmacodynamic drug interactions was investigated in mice and rats, following oral, intragastric, or intraperitoneal administration. Oral ketoconazole (100 mg/kg) potentiated the immunosuppressive action of cyclosporine (25 to 200 mg/kg) in male mice (Anderson *et al.*, 1986). When administered by oral gavage in combination with cyclosporine (10 to 20 mg/kg) ketoconazole (100 mg/kg) also potentiated cyclosporine toxicity (Anderson *et al.*, 1986). In other studies, ketoconazole was shown to prolong the hypnotic effects of methohexital in rats with an ED<sub>50</sub> of 30 mg/kg (Van Cauteren *et al.*, 1990). In another study in rats,

when administered in combination with intravenous midazolam, intragastric ketoconazole treatment had no effect on the pharmacologic action of midazolam; however, ketoconazole treatment significantly increased the  $EC_{50}$  of midazolam (Kotegawa et al., 2002). In a separate study, a ketoconazole dose of 40 mg/kg had no effect on the hypoglycemic effect of glycosides in rats (NDA 18-533). Oral administration of 25 mg/kg had a slight effect on the anticoagulant activity of acenocoumarin when administered for up to 5 days. No effect on coagulation activity of acenocoumarin was seen when ketoconazole was administered in combination with this drug (NDA 18-533).

These effects were noted at high levels of systemic exposure and are not thought to be relevant to dermal application.

### **2.6.3 PHARMACOLOGY TABULATED SUMMARY**

This section is not applicable.

### **2.6.4 PHARMACOKINETICS/TOXICOKINETICS**

#### **2.6.4.1 Brief summary**

A full evaluation of the absorption, distribution, metabolism, and excretion (ADME) of ketoconazole has been conducted. The absorption of topical ketoconazole has been investigated in rats and rabbits following single administration and in mice, rabbits and dogs following repeat administration. Distribution studies of topically administered ketoconazole have not been conducted. It would be expected that such studies would show highest concentrations in the skin, and little or no drug elsewhere in the body given the low systemic concentrations demonstrated in topical PK studies. Although metabolism and excretion studies have not specifically been conducted following topical application, results are expected to be similar to that seen following systemic dosing.

#### **2.6.4.2 Methods of Analysis**

This section is not applicable.

#### **2.6.4.3 Absorption**

Topical absorption of ketoconazole following repeat dose was evaluated in a 90-day toxicity study in CD-1 mice (Study No. MSW00001). Toxicokinetic analysis indicated that systemic exposure to ketoconazole occurred at all dosage levels. However, there was no evidence of accumulation over the 90-day exposure period, and except for the plasma concentration data collected on the first day of dosing, a clear dose-response relationship was not present on Study Days 27 and 89. The absence of a clear dose-response relationship and variability on the toxicokinetic data are not unusual for a dermally applied material and is suggestive of an oral exposure component. Topical absorption of ketoconazole following repeat doses was evaluated in a 28-day dermal irritation study in rabbits (NDA 19-927). Ketoconazole (2%) shampoo was topically applied to the abraded

and intact skin of rabbits (4/sex/dose) in doses of 2 mg/kg, 20 mg/kg, and 50 mg/kg for one hour a day for 28 days. Blood samples were taken 2 hours after the last application on day 28. Using HPLC analysis (limit of quantitation, 5 ng/mL) ketoconazole was not detected in the plasma of any of the treated rabbits. The dermal absorption of ketoconazole was also measured and found to be minimal following repeated vaginal application and after repeated application on the intact and abraded skin of dogs (Absorption of ketoconazole in the dog after repeated vaginal application and after application on the intact and abraded skin, R 41 400/41).

Oral or parenteral administration of ketoconazole was shown to result in substantially higher absorption than that seen following topical administration. In general, following oral dosing, maximal plasma concentrations were reached within an hour or two and concentrations declined rapidly thereafter.

#### 2.6.4.4 Distribution

Distribution studies were conducted in both *in vitro* studies and in *in vivo* studies in rats and guinea pigs following oral or intravenous administration. Following topical administration, distribution similar to that seen after systemic dosing is expected, although at much lower levels.

The distribution of ketoconazole was investigated *in vitro* and in rats and guinea pigs following oral administration. In an *in vitro* study, ketoconazole was found to bind to liver, kidney, lung, and intestinal microsomal proteins (The binding of R 41 400 to human plasma proteins and blood cells, and to subcellular fractions of rat liver, lung, kidney and small intestine, R 41 400/24). In rats, following oral administration, the highest ketoconazole concentrations were seen in the liver and adrenals of males and in **the Harder's gland, adrenals, and liver of females** (Riley and James, 1986). In pregnant rats, oral dosing with ketoconazole resulted in ketoconazole distribution in the placenta and uterus, at higher levels than that of the ovaries, vagina, and fetuses (NDA 18-533). When administered intravenously to pregnant guinea pigs, fetal tissue levels of ketoconazole were substantially lower than that of treated dams (Pharmacokinetics and metabolism of ketoconazole in animals, R 41 400/35). In lactating dogs, oral ketoconazole treatment resulted in small amounts of drug distribution into milk (Ketoconazole (R 41 400) in the beagle dog: transition into the milk. Relation to plasma levels, R 41 400/32; NDA 18-533).

In plasma protein binding studies, ketoconazole was shown to be 98.89% bound to human plasma proteins (The binding of R 41 400 to human plasma proteins and blood cells, and to subcellular fractions of rat liver, lung, kidney and small intestine, R 41 400/24). Blood was obtained from seven healthy male subjects for isolation of blood cell suspensions and plasma. Plasma samples and blood cells samples were incubated separately with [<sup>3</sup>H]-ketoconazole (1.0 µg/mL) for 15 minutes at 37°C. Radioactivity was measured using liquid scintillation spectrometry. The results indicated that in plasma ketoconazole was 98.9% protein bound. In blood, it was determined that 1% of

ketoconazole is present as free drug in plasma fluid, 83.7% is bound to plasma proteins, and 15.3% is distributed to blood cells.

#### **2.6.4.5 Metabolism**

The metabolism of ketoconazole has been investigated following oral dosing in mice, rats and dogs. The metabolic pathway of ketoconazole following topical administration is expected to be similar to that seen following systemic dosing.

Ketoconazole has been shown to be extensively metabolized into numerous inactive metabolites in mice, rats, and dogs (Pharmacokinetics and metabolism of ketoconazole in animals, R41 400/35; A comparison between the excretion and biotransformation of ketoconazole after oral administration in male and female rats, R 41 400/28; Whitehouse *et al.*, 1994; NDA 18-533). The major metabolic pathways involved in the degradation of ketoconazole include oxidative O-dealkylation, oxidizing, splitting, and degrading the imidazole ring, splitting and degrading the piperazine ring, and splitting the dioxolane ring. In male Swiss Webster mice following oral administration of 350 mg/kg/day of ketoconazole for 7 days, ketoconazole was found to be metabolized to 9 different metabolites in the liver. Seven of the metabolites were products of the metabolic alteration of the N-acetylpiperazone ring and two of the metabolites resulted from the oxidation of the imidazole ring. Deacetyl-ketoconazole was the major hepatic metabolite.

#### **2.6.4.6 Excretion**

The excretion of ketoconazole has been investigated in rats and dogs following oral and intravenous administration. Due to low systemic exposure following topical administration, the excretion of topical ketoconazole has not been studied. However, the excretion of ketoconazole following topical application is expected to be similar to that seen following oral or intravenous dosing.

In male and female rats, within 24 hours of dosing, approximately 90% and 78% of the administered ketoconazole dose, respectively was excreted in both the urine and feces, with most excretion occurring via the feces (A comparison between the excretion and biotransformation of ketoconazole after oral administration in male and female rats, Study No. R 41 400/28). In this experiment Wistar rats (4/sex) received a single oral dose of 20 mg/kg and urine and feces were collected for the first 96 hours postdosing. Within 4 days of dosing, both male and female rats excreted at least 95% of the total dose. At 4 days postdosing, urinary excretion of ketoconazole in male rats was 17% whereas urinary excretion in female rats was only 5%. Fecal excretion at 4 days was 81% in males and 90% in females. Only 0.1% of unmetabolized ketoconazole was found in the urine, whereas 4.6% was found in fecal samples.

When the excretion of [<sup>3</sup>H]-ketoconazole in to the urine, feces, and bile of male rats treated intravenously with 5 mg/kg ketoconazole was investigated, over 80% and 16% of intravenously administered ketoconazole was excreted in the feces and urine,

respectively, within 7 days (Rommel *et al.*, 1987). Urinary excretion of ketoconazole was complete by 48 hours post dose, whereas ketoconazole was still being excreted into the feces at 7 days post dosing. The rate of biliary excretion varied from animal to animal. Over the first 6.75 to 7.6 hours after dosing, 20.7% to 53.6% of the dose was excreted in the bile. Over the first 8 to 11 hours post dosing 66.6% to 74.1% of the total administered dose was excreted in bile. These results are relatively consistent with other results indicating that within the first 24 hours of treatment, rats excreted about 60% of the total administered dose in the bile (NDA 18-533).

In a separate study, female beagle dogs were shown to eliminate approximately 80% of the total ketoconazole dose within 48 hours and 92% within 7 days (The excretion and biotransformation of \_\_\_\_\_ (R41400) in the adult beagle dog after oral administration of the \_\_\_\_\_). In this study, two female dogs received a single oral dose of 10 mg/kg [<sup>3</sup>H]-ketoconazole after which urine and feces were collected for 7 days and 6 days, respectively. Using radioactive labeling, 9% of the total ketoconazole dose was found in the urine and 83% was found in the feces. More than half of the drug (55%) found in the feces was unmetabolized ketoconazole.

#### 2.6.4.7 Pharmacokinetic drug interactions

Inhibition of cytochrome P450 enzyme by azole antifungal agents has been well documented in the scientific literature. It is currently known that when administered orally, ketoconazole inhibits cytochrome P450 3A4. Thus when oral ketoconazole is taken in combination with drugs dependent upon cytochrome P450 3A4 enzyme system, increased plasma concentrations of the drug in question generally occurs. In particular, ketoconazole has been found to have interactions with terfenadine, cyclosporine, tacrolimus, methylprednisolone, midazolam, trazolam, digoxin, coumarin-like drugs, phenytoin, rifampin, isoniazid, and loratidine. It is unlikely this interaction would be clinically significant following topical administration of ketoconazole due to its low systemic exposure.

#### 2.6.4.8 Other Pharmacokinetic Studies

Not applicable.

#### 2.6.4.9 Discussion and Conclusions

Studies showed that ketoconazole was rapidly absorbed after oral administration in rats, rabbits, guinea pigs, and dogs. Topical application of ketoconazole in rats, rabbits, and dogs resulted in plasma levels near, below, or slightly above the lower limit of quantitation. Repeat topical administration of ketoconazole in mice resulted in systemic exposure with no evidence of accumulation. The distribution of ketoconazole following oral administration varied with dose and duration of treatment. The liver, adrenals, and **Harder's gland were the tissues containing** maximal concentrations of radioactivity. Ketoconazole is extensively metabolized and is excreted mainly via the feces. As is characteristic of azole antifungal agents, ketoconazole has been shown to cause inhibition

of cytochrome P450 enzymes resulting in prolonged plasma drug levels for drugs whose metabolism and clearance is dependent upon cytochrome P450 enzymes.

An advantage of topical formulations of ketoconazole is the low systemic exposure levels, resulting in formulations that are less likely to cause adverse events in humans.

#### **2.6.4.10 Tables and figures to include comparative TK summary**

Not applicable.

#### **2.6.5 PHARMACOKINETICS TABULATED SUMMARY**

Not applicable.

#### **2.6.6 TOXICOLOGY**

##### **2.6.6.1 Overall toxicology summary**

###### General toxicology:

The toxicity of ketoconazole was investigated in a 28-day study following topical administration in rats (97-003T; submitted/reviewed under IND 57,462 by Dr. Amy Nostrandt). This study was primarily designed to investigate the toxicity of a gel containing a combination of ketoconazole and desonide, but also investigated the toxicity of ketoconazole alone. In this study a gel containing 0 or 40 mg/kg of 2% ketoconazole was applied topically (2 mL/kg) to the shaved backs of Sprague-Dawley — CD@BR rats (10/sex/group) for 6 hours/day. The skin was abraded in half of the animals in each group prior to dosing. Although this study was designed as a 28 day study, the experiment was terminated on days 17 and 18 for all treated females and males, respectively, due to excessive toxicity of desonide. All animals in the control and ketoconazole treated groups survived to study termination. No dermal irritation was observed in control or ketoconazole treated males, but both control (2 slight, 1 moderate) and ketoconazole (4 slight and 2 moderate) treated females exhibited slight to moderate atonia. The NOAEL for ketoconazole was 40 mg/kg when administered alone.

In a 90 day toxicity study in — CD(SD)IGS BR CD-1 mice, ketoconazole gel was topically applied to the skin of 5 groups of mice (10/sex/group) at doses of 0 (placebo gel), 40, 80, 160, and 400 mg/kg

\_\_\_\_\_ An additional set of 54 animals/sex/group were treated (40 to 400 mg/kg) for toxicokinetic analyses. Toxicokinetic analysis revealed that animals were systemically exposed to ketoconazole. No accumulation occurred and a dose-response relationship in plasma drug concentrations was not observed on days 27 and 89. This phenomenon could be due to oral ingestion of compound due to animal grooming. Based on the results of this study, dermal application of ketoconazole to the mouse for up to 17 days (400 mg/kg) or a minimum of 90 consecutive days (40, 80, and 160 mg/kg) did not produce mortality or clinical signs of toxicity. Irritation at the site of test article

application was noted grossly at 160 and 400 mg/kg and microscopically at all dose levels examined (40, 80, and 160 mg/kg). In addition, pigmentation of the liver was observed at all dose levels and a higher incidence of renal hypertrophy was noted microscopically in the 80 and 160 mg/kg animals. Thyroid glands were also noted to be slightly heavier in all treated male groups (40, 80, and 160 mg/kg). However, microscopic examination of this organ did not reveal any notable structural changes so the biologic relevance of this change was unclear. Therefore, based on the above findings, a NOEL was not obtained for this study.

In a 21-day study 2% ketoconazole cream was topically applied to abraded and non-abraded skin on the backs of New Zealand White rabbits (Study No. 2245; submitted/reviewed under IND 57,462 by Dr. Amy Nostrandt). After three weeks of treatment (5 days/week) with 2 g/kg of vehicle cream, desonide 0.05% cream, ketoconazole 2% cream or ketoconazole 2%/desonide 0.05% cream, the only significant findings were decreased spleen weight in treated females and histopathological changes in the adrenals, liver, and thymus, particularly in males, in groups treated with desonide. All control and ketoconazole treated animals survived to study termination. Ketoconazole treatment had no adverse effects on bodyweights, hematology, gross pathology, histopathology, and did not cause dermal irritation (Draize Score: 0). Thus the NOAEL was determined to be 40 mg/kg of ketoconazole.

The toxicity of ketoconazole was investigated in a 28-day study following dermal administration in rabbits (97-002T; submitted/reviewed under IND 57,462 by Dr. Amy Nostrandt). This study was primarily designed to investigate the toxicity of a gel containing a combination of ketoconazole and desonide, but also investigated the toxicity of ketoconazole alone. In this study a gel containing 0 or 40 mg/kg of 2% ketoconazole was applied topically (2 mL/kg) to the skin of 10 rabbits/sex/group for periods of 6 hours/day. The skin was abraded in half of the animals in each group prior to dosing. There was no mortality noted during the study. Animals treated with ketoconazole had no treatment-related effects on clinical signs, body weights, feed consumption, clinical pathology, or ophthalmology. At necropsy there were no treatment-related macroscopic or microscopic observations. Toxicokinetic analysis revealed that mean ketoconazole plasma concentrations were below the detectable limits (10 ng/mL) on Day 1 for males and females and on Day 27 for females. On Day 27, mean ketoconazole plasma **concentrations for males (12.3 – 12.6 ng/mL)** were slightly above detectable limits. Mean Draize irritation scores ranged from 0.4 to 0.7 on day 15 but by Day 30, scores were 0. The NOAEL for ketoconazole was 40 mg/kg/day when applied dermally to rabbits.

The toxicity of ketoconazole was investigated in a 28-day study in minipigs following dermal administration (98-013T; submitted/reviewed under IND 57,462 by Dr. Amy Nostrandt). This study was primarily designed to investigate the toxicity of a gel containing a combination of ketoconazole and desonide, but also investigated the toxicity of ketoconazole alone. In this study, ketoconazole gel (240 mg/kg) was dermally applied to the nonabraded skin of groups of 3 animals/sex for 6 hours/day (7 days a week) for up to 29 or 30 days. During treatment test sites were bandaged and after treatment

bandages were removed and residual test material was washed away. Blood samples were taken for clinical chemistry and hematology evaluations before treatment and during weeks 3 and 5 and for toxicokinetic analyses at 3, 6, and 24 hours after dosing on study Days 1 and 28. Topical administration of 240 mg/kg of ketoconazole gel did not result in any treatment related adverse effects on survival, bodyweights, organ weights, feed consumption, heart or respiration rate, ophthalmology, dermal irritation, gross pathology, or histopathology. With the exception of transient excessive salivation noted for 1 to 2 days in one treated male, topical administration of 240 mg/kg of ketoconazole gel did not result in any treatment related adverse clinical signs. Very slight erythema was evident for 1 to 2 days in 3 males and 1 female treated with ketoconazole while control animals exhibited very slight erythema for 3 to 14 days. Therefore it was concluded that there were no treatment-related effects on dermal irritation. Toxicokinetic analysis demonstrated that ketoconazole was not detected in the plasma at any timepoint on Day 1 and was below or slightly above the limit of detection at 6 and 24 hours post dosing on Day 28. The NOAEL for ketoconazole was 240 mg/kg.

#### Genetic toxicology:

When tested in the Ames assay, ketoconazole alone was found to be non-mutagenic to *Salmonella typhimurium* in the presence and absence of metabolic activation (NDA 18-533). A complete battery of genotoxicity studies of 2% ketoconazole were performed in combination with desonide. In an Ames assay, 2% ketoconazole and 0.05% desonide (Study no. 98-001T; submitted/reviewed under IND 57462 by Dr. Amy Nostrandt), the ketoconazole-desonide combination product, did not significantly increase the number of revertant colonies in the presence or absence of S9 metabolic activation, and the study was considered negative. An *in vitro* study evaluating the potential for 2.0% ketoconazole and 0.05% desonide gel to induce chromosomal aberrations in Chinese hamster ovary cells was also conducted (Study no. 98-003T; submitted/reviewed under IND 57462 by Dr. Amy Nostrandt). Although there was no significant increase in chromosomal aberrations or polyploidy there was an increase in endoreduplication at 10/0.25 and 20/0.5 µg/mL ketoconazole/desonide with metabolic activation (8.5% and 11%, respectively). Additionally, cytotoxicity was insufficient (as per ICH genotoxicity guidelines S2A, section 2.1.2.2) and higher concentrations should have been analyzed. When tested in an *in vivo* mouse micronucleus study the ketoconazole and desonide combination (Study no. 98-002T; submitted/reviewed under IND 57462 by Dr. Amy Nostrandt) was negative with the exception of one (of six) mouse with a clearly positive response at the high dose of the drug product at 48 hours. A second mouse micronucleus test for the ketoconazole/desonide combination (Study no. 98-017T) was subsequently conducted and is reviewed below. The results of this second study were considered negative for the detection of clastogenicity.

#### Carcinogenicity:

Ketoconazole was found to be noncarcinogenic in an 18 month feeding study in mice and in a 2-year feeding study in rats (NDA 18-533; NDA 19-927). Ketoconazole gel did not induce photocarcinogenicity when evaluated in a 12-month photocarcinogenicity study in

mice (Study report no. T99-013; submitted/reviewed under IND \_\_\_\_\_ Dr. Jill Merrill). In short term tumor growth studies in mice, ketoconazole treatment was shown to significantly delay the formation of tumors and prolong survival in C57BL/6(B6) mice and to have no effect on tumor formation in athymic mice (Naftalovich *et al.*, 1991; Shaughnessey *et al.*, 1994). In an *in vitro* study, ketoconazole was shown to inhibit the growth of human tumor cells (fibrosarcoma cells) (Shaughnessey *et al.*, 1994). The sponsor has agreed to conduct a mouse dermal carcinogenicity study as a phase 4 commitment. The protocol has been submitted (IND \_\_\_\_\_ SN0036) and reviewed by the eCAC (meeting minutes attached), but the sponsor has subsequently decided to delay the start of the study until they receive NDA approval.

#### Reproductive toxicology:

The reproductive and developmental toxicology of ketoconazole was studied in fertility and embryonic studies on rats, dogs, and monkeys, in embryofetal development studies in mice, rats, and rabbits, and in pre- and postnatal development studies in rats. When the effect of ketoconazole on fertility and embryonic development was studied in rats, ketoconazole doses of  $\leq 40$  mg/100 g of feed had no teratogenic effects, and no effects on fertility, gestation, or pup viability (NDA 18-533). Ketoconazole doses of 80 mg/kg caused maternal toxicity, mortality, and embryotoxicity, increased resorptions, and teratogenicity (missing metacarpal and metatarsal bones, and abnormal heads). In fertility studies in male rats, oral ketoconazole treatment (24, 75, or 300 mg/kg) generally resulted in reduced sperm motility, reduced plasma testosterone levels, increased amounts of abnormal sperm, and decreased pregnancy rates but did not cause any adverse effects in untreated females or fetuses (Delongas *et al.*, 1995; Vawda and Davies, 1986; Wang *et al.*, 1992). In female rats, ketoconazole treatment ( $\geq 75$  mg/kg) during the first few days of gestation (DG 1-8) resulted in significant reductions in serum progesterone levels (Cummings and Metcalf, 1996; Cummings *et al.*, 1997). In male beagle dogs, oral ketoconazole treatment (25 mg/kg) for up to 4 weeks caused a decrease in sperm motility, sperm count, an increase in the number of abnormal sperm, and atrophy of the testes all of which were reversed after treatment was withdrawn (Delongas *et al.*, 1996). In monkeys, sperm motility decreased following oral ketoconazole (85-100 mg/kg) administration (Vickery *et al.*, 1985).

When the effect of ketoconazole on embryofetal development was studied in mice, doses of 20 mg/kg and higher caused increased resorptions and stillbirths and 40 mg/kg caused decreased birth weight (Buttar *et al.*, 1989). In rats, teratogenicity and other effects (embryotoxicity, decreased pregnancy rates, increase in dead fetuses, etc.) were observed in litters of dams treated with maternally toxic ketoconazole doses of 80 mg/kg and higher (NDA 18-533). In rabbits, no teratogenicity was observed after oral doses of 40 mg/kg, however, pregnancy rates were decreased and the mortality rate was increased (NDA 18-533).

In pre- and postnatal development studies in female rats, ketoconazole doses of  $\geq 40$  mg/kg caused maternal toxicity as evidenced by mortality, decreased body weights, feed

consumption, or decreased pregnancy rates. These doses were also toxic to the offspring, resulting in decreased pup weights, and viability (NDA 18-533).

Special toxicology:

A primary eye irritation study with ketoconazole 2% gel was conducted in rabbits (MSW00017) and is reviewed below.

**2.6.6.2 Single-dose toxicity**

No single-dose toxicity studies were submitted to this NDA.

**2.6.6.3 Repeat-dose toxicity**

No new repeat-dose toxicity studies were submitted to this NDA.

**2.6.6.4 Genetic toxicology**

**Study title:** Mutagenicity test on ketoconazole:desonide (40:1 ratio) in the *in vivo* mouse micronucleus assay

**Key findings:** Ketoconazole:desonide (40:1 ratio) did not induce a statistically significant increase in the frequency of micronucleated PCEs and is considered negative in the mouse bone marrow micronucleus assay under the conditions of this assay.

**Sponsor Study no.:** 98-017T

**Laboratory Study no.:** 19582-0-455OECD

**Volume #, and page #:** electronic

**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** July 6, 1998

**GLP compliance:** Yes

**QA reports:** yes ( x)

**Drug, lot #, and % purity:** ketoconazole, lot # 96K201, control # 8445-84  
desonide, lot # 00012720, control # 8847-079

**Methods**

Strains/species/cell line: — CD-1® (ICR) BR mouse

Dose selection criteria:

Basis of dose selection: based on dose range finding study where it was determined the MTD was estimated to be 1400:35 mg/kg for males and 1500:37.5 mg/kg for females

Test agent stability: not provided

Metabolic activation system: *in vivo* study

Controls:

Vehicle: corn oil \_\_\_\_\_ lot # 12-354)

Negative controls: vehicle

Positive controls: Cyclophosphamide (CP: CAS # 6055-19-2; \_\_\_\_\_ Lot #87H0207) served as the positive reference compound. It was administered orally at a single dose of 80 mg/kg.

#### Exposure conditions:

Incubation and sampling times: Animals were dosed by gavage and bone marrow was harvested at 24 hours in all groups and also at 48 hours in the high dose and vehicle control groups.

Doses used in definitive study: males: 350:8.75, 700:17.5, 1400:35 mg/kg of ketoconazole:desonide (40:1); females: 375:9.375, 750:18.75, 1500:37.5 mg/kg of ketoconazole:desonide were administered by gavage.

#### Study design:

Dosing Scheme for Micronucleus Study

Target Treatment (mg/kg)	Route of Administration	Dosing Volume (ml/kg)	Animals/Harvest Timepoint		Replacement Animals*	
			24 Hour	48 Hour	M	F
Ketoconazole:Desonide (40:1 ratio) for the males/females, respectively						
350:8.75 / 375:9.375	PO	5	6	6	-	-
700:17.5 / 750:18.75	PO	10	6	6	-	-
1400:35 / 1500:37.5	PO	20	6	6	6	6
Vehicle Control, corn oil	PO	20	6	6	6	6
Positive Control, Cyclophosphamide, 80.0	PO	10	6	6	-	-

\* The animals assigned to the secondary dose groups were dosed only as potential replacements for animals which died in the original high dose group. All animals not used as replacements were euthanized at the completion of the trial.

Animals were observed at least once daily. At the harvest timepoints mice were euthanized by CO<sub>2</sub> inhalation followed by incision of the diaphragm. Bone marrow cells were flushed from the tibias or femurs of the first five surviving animals in each group.

Slides were fixed in methanol and stained in May-Grünwald Solution followed by Giemsa stain.

#### Analysis:

- 5/group/timepoint
- The slides were analyzed by scoring 2000 polychromatic erythrocytes (PCE) from each animal.
- The PCE to normochromatic erythrocyte (NCE) ratio was calculated. At least 200 erythrocytes per animal were counted to determine the PCE:NCE.
- **The mean percent micronucleated PCE's and the mean PCE:NCE ratio were calculated for each treatment.**

Criteria for positive results: A statistically significant ( $p \leq 0.05$ ) increase in micronucleated PCEs for at least one dose level, and a statistically significant ( $p \leq 0.05$ ) dose-related response. Both of these responses were required for a

positive finding. The study director also considered the biological relevance of the results in the final evaluation.

**Summary of individual study findings:**

**Study validity:** The study acceptance criteria were that the vehicle control group should have less than approximately 0.4% micronucleated PCEs and the positive control group should have a statistically significantly higher incidence of micronucleated PCEs ( $p < 0.01$ ) than the vehicle control group. The criteria were met and the study was considered valid.

**Study outcome:** Ketoconazole:desonide (40:1 ratio) induced signs of clinical toxicity in treated animals but was not cytotoxic to the bone marrow (i.e., no statistically significant decrease in the PCE:NCE ratio). Ketoconazole:desonide (40:1 ratio) induced no statistically significant increases in micronucleated PCEs over the levels observed in the vehicle controls at any of the harvest timepoints. The positive control resulted in a statistically significant increase in the frequency of micronucleated PCEs as compared to the vehicle controls, with means and standard errors of  $3.64\% \pm 0.37\%$  and  $2.54\% \pm 0.43\%$  for the males and females, respectively.

**2.6.6.5 Carcinogenicity**

No carcinogenicity studies were included in this NDA submission.

**2.6.6.6 Reproductive and developmental toxicology**

No reproductive and developmental toxicology studies were included in this NDA submission.

**2.6.6.7 Local tolerance**

No local tolerance studies were included in this NDA submission.

**2.6.6.8 Special toxicology studies**

**Study title:** A primary eye irritation study in rabbits with Ketoconazole USP 2% topical gel

**Key study findings:** Based on the results of this test, both the placebo gel and ketoconazole 2% gel were mild irritants. All irritation reversed by 72 hours after treatment.

**Study no.:** MSW00017

**Volume #, and page #:** electronic document

**Conducting laboratory and location:** \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Date of study initiation:** September 21, 2004

**GLP compliance:** Yes

**QA reports:** yes (x)

**Drug, lot #, and % purity:**

ketoconazole USP 2% topical gel, Lot # UEBM-C, \_\_\_\_\_

**Formulation/vehicle:** placebo gel, Lot # UHEN-C, purity not provided

## Methods

**Doses:** all rabbits received a single 0.1 mL dose of either the test article or placebo gel in the conjunctival sac of the right eye.

## Study Design:

Group	Treatment	No. of Animals		Dose Volume (mL)
		Male	Female	
1-No Rinse	Ketoconazole USP 2% Topical Gel	2	1	0.1
2-Rinse	Ketoconazole USP 2% Topical Gel	3	0	0.1
3-No Rinse	Placebo Gel	3	0	0.1
4-Rinse	Placebo Gel	3	0	0.1

Approximately 30 seconds after instillation of the test article/placebo, the test and control eyes of Groups 2 and 4 were rinsed with sterile water for approximately 30 seconds to remove the test article/placebo using a volume and velocity of flow which did not cause injury. Group 1 and 3 eyes were not rinsed. The contralateral eye of each animal remained untreated and served as a control.

Test and control eyes were examined with the aid of an auxiliary light source for signs of irritation at 1, 24, 48, and 72 hours after dosing according to the Ocular Grading System which is based on Draize.

## Results: Group 1 –Ketoconazole USP 2% Topical Gel – No Rinse

Exposure to the test article produced corneal opacity in 2/3 test eyes by the 24-hour scoring interval which was confirmed by positive fluorescein dye retention. The corneal opacity resolved completely in the affected eyes by the 48-hour scoring interval. Iritis was noted in 2/3 test eyes at the 1-hour scoring interval which resolved completely in both the affected test eyes by the 24-hour scoring interval. Conjunctivitis (redness, swelling, and discharge) was noted in 3/3 test eyes at the 1-hour scoring interval. The conjunctival irritation resolved completely in 1/3 test eyes by the 48-hour scoring interval and in the remaining 2/3 test eyes by the 72-hour scoring interval. Additional ocular findings noted during the study included sloughing of the corneal epithelium (1/3 test eyes) and slight dulling of the normal luster of the cornea (1/3 test eyes).

**Group 2 –Ketoconazole USP 2% Topical Gel – Rinse**

Exposure to the test article produced conjunctivitis (redness and swelling) that was noted in 3/3 test eyes at the 1-hour scoring interval which resolved completely in 3/3 test eyes by the 72-hour scoring interval. An additional ocular finding of slight dulling of the normal luster of the cornea (1/3 test eyes) was noted during the study.

**Group 3 – Placebo Gel – No Rinse**

Exposure to the placebo produced conjunctivitis (redness and swelling) that was noted in 3/3 test eyes at the 1-hour scoring interval which resolved completely in 1/3 test eyes by the 48-hour scoring interval and in the remaining 2/3 test eyes by the 72-hour scoring interval.

**Group 4 – Placebo Gel – Rinse**

Exposure to the placebo produced iritis in 1/3 test eyes at the 1-hour scoring interval and resolved completely by the 24-hour scoring interval. Conjunctivitis (redness, swelling and/or discharge) was noted in 3/3 test eyes at the 1-hour scoring interval which resolved completely in 3/3 test eyes by the 72-hour scoring interval. An additional ocular finding of slight dulling of the normal luster of the cornea (1/3 test eyes) was noted during the study.

Based on the data from this study, the test results for Ketoconazole USP 2% Topical Gel and Placebo Gel are presented below:

Group	Maximum Average Score	Treatment	Kay and Calandra Classification	CPSC Classification
1-No Rinse	16.00	Ketoconazole USP 2% Topical Gel	Mild Irritant	Equivocal
2-Rinse	6.00	Ketoconazole USP 2% Topical Gel	Mild Irritant	Positive
3-No Rinse	6.00	Placebo Gel	Mild Irritant	Negative
4-Rinse	9.00	Placebo Gel	Mild Irritant	Positive

A comparison of the groups indicated that Group 1 had a slightly higher Maximum Average Score (16.00) than the other groups. However, the duration and severity of the irritation varied throughout the groups. All irritation cleared by 72 hours, making the Ketoconazole 2% Topical gel and the Placebo Gel mild irritants, as per the Kay and Calandra classification. The CPSC classification depended on the number of animals with a positive response at any of the 24, 48 or 72 hour readings.

**2.6.6.9 Discussion and Conclusions**

The sponsor has completed a repeat dose dermal toxicity study in mice and submitted a protocol for a 2-year dermal carcinogenicity study for review by the eCAC (meeting minutes attached). However, the sponsor has subsequently informed the Agency that they do not intend to start the dermal carcinogenicity study until they receive approval for

this NDA. At such time the sponsor will submit a timeline, detailing the expected study start date as well as an expected date for submitting the study results to the Agency for review by the eCAC.

#### **2.6.6.10 Tables and Figures**

Not applicable.

#### **2.6.7 TOXICOLOGY TABULATED SUMMARY**

Not applicable.

### **OVERALL CONCLUSIONS AND RECOMMENDATIONS**

**Conclusions:** Based on the nonclinical data available for ketoconazole, NDA 21-946 is approvable from a pharmacology/toxicology perspective.

**Unresolved toxicology issues (if any):** The dermal carcinogenicity study is planned as a phase 4 commitment and will be initiated after the sponsor receives Agency approval for NDA 21-946. Otherwise, there are no unresolved toxicology issues at this time.

**Recommendations:** The sponsor-proposed labeling has been revised and the revised nonclinical portions are provided in the next section. The calculations for human dose multiples are provided as an appendix.

#### **Suggested labeling:**

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies to assess the carcinogenic potential of TRADENAME Gel have not been conducted. A long-term feeding study in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity. Ketoconazole gel at a dosage up to 5 mg/kg/dose is not photocarcinogenic when topically applied to hairless mice 5 days/week for a period of 40 weeks. Ketoconazole produced no evidence of mutagenicity in the dominant lethal mutation test in male and female mice at single oral doses up to 80 mg/kg. When tested in the Ames assay, ketoconazole was found to be non-mutagenic to *Salmonella typhimurium* in the presence and absence of metabolic activation. Ketoconazole, in combination with another drug, gave equivocal results in the mouse micronucleus test. At oral dose levels of 75-80 mg/kg/day (71 to 76 times the human dose) ketoconazole impaired the reproductive performance in female (decreased pregnancy and implantation rates) and male (increased abnormal sperm and decreased sperm motility) rats.

**Pregnancy Category C:** Reproductive toxicity studies have not been performed with TRADENAME Gel. Ketoconazole was tested for its effects on offspring in the rat at oral doses of 10, 20, 40, 80 and 160 mg/kg. Ketoconazole was teratogenic (syndactylia and oligodactylia) at 80 mg/kg/day and embryotoxic at 160 mg/kg/day (76 and 152 times the human dose, respectively). However, these effects may be related to maternal toxicity, which was also seen at these dose levels.

**Nonteratogenic effects:** Doses of 10, 20, 40, 80, and 160 mg/kg were studied in pre- and postnatal development studies in rats. Doses of 40 mg/kg (38 times the human dose) and above were associated with maternal toxicity, an increase in the length of gestation, and an increase in the number of stillborn fetuses. These doses of ketoconazole were also toxic to the offspring, resulting in a decrease in fetal/pup weights and viability.

There are no adequate and well controlled studies in pregnant women. TRADENAME Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Signatures (optional):

Reviewer Signature \_\_\_\_\_

Supervisor Signature \_\_\_\_\_ Concurrence Yes \_\_\_ No \_\_\_

## APPENDIX/ATTACHMENTS

### Calculation of Human Dose Multiples

20 mg/g = 2% ketoconazole

7.16 grams of product used over 14 days

This equals 7.16 g / 14 days = 0.511 g/day

0.511 g/day x 20 mg/g = 10.22 mg ketoconazole/day

10.22 mg / 60 kg = 0.1705 mg/kg

75 - 80 mg/kg/day in rats

75 x 6/37 = 12.162 mg/kg (HED)

80 x 6/37 = 12.973 mg/kg (HED)

160 mg/kg/day (rats)

160 x 6/37 = 25.95 mg/kg (HED)

### Multiples of human dose

12.162 / 0.1705 = 71.33

12.973 / 0.1705 = 76.09

25.95 mg/kg / 0.1705 mg/kg = 152.18

### Sponsor-proposed labeling

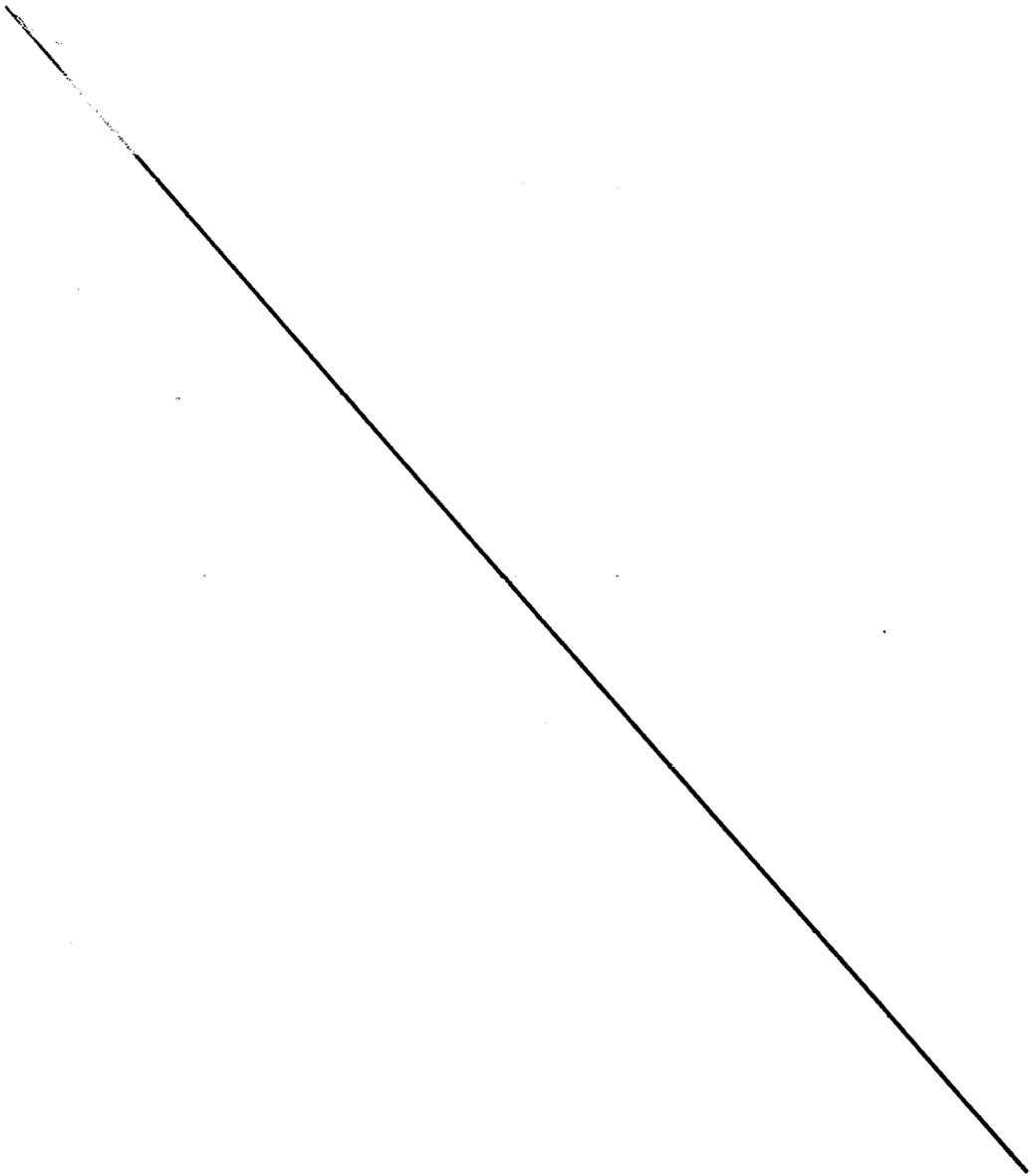
5 Page(s) Withheld

       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

Withheld Track Number: Pharm/Tox- 1/1



***EXECUTIVE CAC***

**DATE OF MEETING: 11/29/05**

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair  
Joseph Contrera, Ph.D., OPS, Member  
Abby Jacobs, Ph.D., OND IO, Member  
Josie Yang, D.V.M, Ph.D., DAARP, Alternate Member  
Paul Brown, Ph.D., DDDP, Supervisor  
Jill Merrill, Ph.D., DDDP, Presenting Reviewer

**AUTHOR OF DRAFT: JILL MERRILL**

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

**The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay.** The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

**IND# 67,820****Drug Name:** Ketoconazole 2% gel**Sponsor:** Barrier Therapeutics, Inc.**Background:**

Ketoconazole is a synthetic, substituted imidazole derivative with broad spectrum antimycotic activity. It inhibits the synthesis of ergosterol, a cholesterol-like substance, a key component of fungal cell membranes. By blocking the synthesis of ergosterol, ketoconazole causes cell membrane disruption and leads to fungal cell death. It was first approved for oral human use to treat systemic mycotic infections in 1981. A topical cream containing 2% ketoconazole was approved under NDA 19-084 in 1985 for the treatment of tinea corporis, tinea cruris, tinea pedis, tinea (pityriasis) versicolor, cutaneous candidiasis, and seborrheic dermatitis. Since patients with seborrheic dermatitis may require repeated treatment over a long period, it is appropriate to assess the carcinogenicity of this drug. Ketoconazole was not genotoxic in a standard battery of genetic toxicity tests.

***MOUSE CARCINOGENICITY STUDY PROTOCOL AND DOSE SELECTION:***

The sponsor proposed a two year dermal carcinogenicity study in mice with the following parameters.

Species/strain: Mouse — CD-1@(ICR)BR VAF Plus

Number/sex/dose: 65/sex/dose

Route: dermal application

**Male and female**

Doses proposed: 0 (vehicle control), 10 (0.125%), 20 (0.25%), 40 (0.5%) mg/kg

The drug article will be administered daily which mimics the proposed clinical dosing regimen.

Complete histopathology in all groups is proposed. The sponsor proposes a toxicokinetic phase with an additional 50 animals/sex/group.

The sponsor conducted a 13-week dermal toxicity and toxicokinetic study with ketoconazole topical gel in mice. Male and female mice were treated daily with ~ 0, 40,

80, 160 or 400 mg/kg/day in a fixed dose volume of 200  $\mu$ L. The formulations used consisted of the clinical vehicle containing 0, 0.5, 1, 2 and 5% ketoconazole, respectively.

The 2% Formulation is provided in the following table. Other formulations were similar except for the changes in ketoconazole concentration and corresponding alcohol percentages.

Ingredient	Weight %	
Ketoconazole	2.0%	
Polyethylene glycol 400		
Propylene glycol, USP		
Glycerin, USP		
PPG-15 Stearyl ether		
Hydroxypropyl cellulose		
Ascorbic acid, USP		
Butylated hydroxytoluene		
Citric acid monohydrate, USP		
Alcohol		34.0%
FD&C Yellow No. 6		
D&C Yellow No. 10		

Assessment of toxicity was based on mortality, clinical observations, dermal observations, body weights, feed consumption, and clinical and anatomic pathology evaluations.

Animals treated with 400 mg/kg/day were euthanized on Day 17 due to severe dermal irritation. There were no test article-related mortalities within the remaining animals (treated with up to 160 mg/kg/day). Significant dermal irritation and epidermal hyperplasia was noted in the 160 mg/kg group. A dose-related increase in the incidence of minimal to mild hypertrophy of individual epithelial cells in the collecting ducts was noted in the kidneys. Based on the dermal observations in the 90-day dermal study, the sponsor believes 160 mg/kg/day exceeded the MTD and that the renal changes noted at 80 mg/kg/day and 160 mg/kg/day would not be tolerated over 2 years. For these reasons they propose a high dose of 40 mg/kg/day.

***EXECUTIVE CAC RECOMMENDATIONS AND CONCLUSIONS:***

- The Committee recommended doses of 0 (untreated), 0 (vehicle), 20, 40, and 80 mg/kg administered daily by dermal application based on MTD (dermal irritation at 160 mg/kg). The corresponding ketoconazole concentrations are 0, 0, 0.25, 0.5, and 1.0% (w/w), making the highest concentration half of the proposed clinical formulation.
- It is recommended that the sponsor include both an untreated control as well as a vehicle control group.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

cc:

/Division File, DDP  
/PBrown/Supervisor, DDDP  
/JMerrill/Reviewer, DDDP  
/MAAnderson/PM, DDDP  
/ASeifried, OND IO

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added human dose multiples as appendix

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