CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-738

<u>PHARMACOLOGY REVIEW</u>

Pharmacology/Toxicology Memorandum

NDA number: 21-738
Sequence number/date/type of submission: N000/ 11 December 2006/AZ
Sponsor and/or agent: Connetics Corporation
                    3290 West Bayshore Road
                    Palo Alto, CA 94303
Reviewer name: Paul C. Brown
Division name: Division of Dermatology and Dental Products
Review completion date: June 1, 2007

Drug: ketoconazole foam, 2%

Introduction:
NDA 21-738 was originally submitted under section 505(b)(2) of the FD&C Act with a letter date of 23 January 2004. The NDA was found to be not approvable and a letter indicating this was sent to the sponsor on 23 November 2004. The sponsor has now submitted a response to the not approvable letter. There were no pharmacology/toxicology issues in the not approvable letter. No new nonclinical data was submitted in this resubmission.

In the original NDA the sponsor submitted data from clinical studies in which their new foam product was compared to Nizoral Cream 2%. In this study the ketoconazole foam 2% was non-inferior to Nizoral Cream 2% but it was not superior to the vehicle foam. The not approvable letter recommended that another study would need to be submitted demonstrating superiority of ketoconazole foam 2% to its vehicle and non-inferiority to the comparator. The current submission contains a report of a study in which the ketoconazole foam 2% was compared to its vehicle and to ketoconazole cream 2% manufactured by Teva. This study did not use Nizoral Cream 2% since this product is apparently no longer marketed. The Teva product is a generic that referred to Nizoral Cream 2%.

The sponsor also conducted a comparative bioavailability study of the ketoconazole foam formulation and Nizoral Cream 2%. The clinical pharmacology and biopharmaceutics reviewer found that overall, absorption of ketoconazole in subjects treated with ketoconazole foam was higher than in subjects treated with Nizoral Cream; however, these levels of ketoconazole are significantly lower than levels observed following oral administration of ketoconazole. No comparative bioavailability study was conducted with the foam and the Teva product; however, since the Teva product is a generic form of Nizoral the clinical bridge to these products appears adequate to permit reference to the Agency's finding of safety for Nizoral Cream. From a pharmacology and toxicology perspective, this finding of safety is adequate to support the approval of the ketoconazole foam product.

The chemistry review has noted that

Labeling recommendations:
Suggested wording for the nonclinical portions of the labeling is provided below.

/s/

Paul Brown
6/1/2007 11:33:27 AM
PHARMACOLOGIST

memo to close pharm/tox review of NDA resubmision

Susan Walker
6/1/2007 01:23:41 PM
DIRECTOR

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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: 21-738

SERIAL NUMBER: 000

DATE RECEIVED BY CENTER: 01/26/04

PRODUCT: Extina^{TM}

INTENDED CLINICAL POPULATION: Adults

SPONSOR: Connetics Corporation

                                Palo Alto, CA

DOCUMENTS REVIEWED: Vol. 1.1-1.4

REVIEW DIVISION: Division of Dermal and Dental Drug Products

                                (HFD-540)

PHARM/TOX REVIEWER: Kumar D. Mainigi

PHARM/TOX SUPERVISOR: Paul Brown

DIVISION DIRECTOR: Jonathan Willkin

PROJECT MANAGER: Virginia Giroux

Date of review submission to Division File System (DFS): 08-05-2004

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EXECUTIVE SUMMARY

1. Recommendations

1.1   Recommendation on approvability: Approvable

1.2   Recommendation for non-clinical studies: Accepted to support the drug safety

1.3   Recommendations on labeling: Acceptable with modifications

2   Summary of non-clinical findings

2.1   <u>Brief overview of non-clinical findings</u>: Because of restrictions on the use of previously evaluated data for the same active ingredient from a different sponsor, the information about the non-clinical safety of the proposed formulation submitted under section 505 (b) (2) is drawn from the published reports and the labels of approved ketoconazole (KTZ) products. No animal studies were conducted with Extina™ (Ketoconazole Foam, 2%).

In 4-week dermal studies using abraded and intact sites in rabbits (40mg/kg/day) and dogs (80mg/kg/day), absolutely no systemic or local toxicity was observed. The plasma drug levels in both cases were below the detection limit of 2ng/mL. The dose levels of 40 and 80mg KTZ/kg were established as dermal NOAELs (no observed adverse effects level) for rabbit and dog, respectively.

In a 4-week clinical study where patients with moderate to severe seborrheic dermatitis received daily topical applications of 120mg of KTZ from the proposed 2% foam formulation, the average plasma drug level was 6ng/mL.

In a number of genotoxicity studies, ketoconazole did not express any mutagenic or clastogenic potentials. In two oral carcinogenicity studies (5, 20, and 80mg/kg/day) in rats and mice, ketoconazole tested non-carcinogenic. In rat oral studies, ketoconazole was established as teratogenic and embryotoxic at 40 to 80mg/kg/day dose levels; the reproductive performance in both the sexes was also impaired.

Taking into account, complete absence of any systemic or local toxicity in the multiple animal species at dose levels much greater than the expected daily human dose, and less than 1% dermal absorption of KTZ both in animals and humans, a sound clinical safety profile for the foam formulation has emerged.

2.2   <u>Pharmacologic activity:</u> The primary pharmacologic (anti-fungal) activity of KTZ leads to a disformed and dysfunctional cytoplasmic membrane in the fungus. The fungistatic action involves the inhibition of cytochrome P450

enzyme 14 α-demethylase, resulting in blocking the synthesis of lanosterol, a critical structural component of the membrane. The secondary pharmacologic (anti-inflammatory) activity of KTZ is directed at the inhibition of 5-lipooxygenase, the enzyme catalyzing the formation of leukotriene B4 from the arachidonic acid component of the membrane. The sponsor proposes that the combined primary and secondary pharmacologic activities of KTZ would be effective in the treatment of seborrheic dermatitis.

2.3   Nonclinical safety issues relevant to clinical use: None

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PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY:

Ketoconazole (KTZ) a broad-spectrum synthetic imidazole antifungal agent is used both orally and topically. Its oral and 2% topical formulations were approved in 1981 and 1985, respectively, and 2% shampoo for dandruff was approved in 1990. In addition, a generic topical cream was cleared for marketing in 2000, and 1% over-the-counter shampoo for dandruff was approved in 1997. Janssen Pharmaceutical markets these products under the trade name Nizoral[R].

Topically, the drug has been used to treat seborrheic dermatitis, tinea corporis, tinea cruris, tinea pedis, tinea versicolor, and cutaneous candidiasis. The oral formulations have been used to treat candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidiodomycosis, histoplasmosis, chromomycosis, ring worm, *Candida* vulvovaginitis, esophageal candidiasis, and paracoccidioidomycosis.

The proposed topical formulation Extina[TM] (Ketoconazole Foam, 2%) submitted under section 505 (b) (2) is aimed to treat seborrheic dermatitis.

NDA number: 21-738
Review number: 01
Sequence number/date/type of submission: N000/01-26-04/original,
                                    BZ/04-28-04, and BP/06/1/04
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Connetics Corporation
                    3290 West Bayshore Road
                    Palo Alto, CA 94303
Manufacturer for drug substance:

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

Drug:
   Trade name: **Extina**[TM] (Ketoconazole Foam, 2%)
   Generic name: Ketoconazole
   Code name:
   Chemical name: Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1 *H*-imidazol-1-ylmethyl)-1, 3-dioxolan-4-yl] methoxy] phenyl]-, *cis*-
   CAS registry number: 65277-42-1
   Molecular formula/molecular weight: $C_{26}H_{28}Cl_2N_4O_4$/531.43

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Structure:

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Relevant INDs/NDAs/DMFs:
INDs: NDAs:

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Drug class: Antifungal
Indication: Seborrheic dermatitis

Clinical formulation: 2% Aerosol Foam

Component[a]	Function	Percent(w/w)[b]
Ketoconazole, USP	Active ingredient	2.00
Excipients		
Cetyl alcohol, NF		
Denatured alcohol		
Citric acid, USP		
Polysorbate 60, NF		
Potassium citrate, USP		
Propylene glycol, USP		
Purified water, USP		
Stearyl alcohol, NF		

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b Concentration/can

Route of administration: Topical

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

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Data reliance: The information or data necessary for approval of NDA 21-738 submitted by Connetics Corporation, Palo Alto, CA is drawn from the following: (1) published literature, and (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Connetics Corporation does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for the approval of NDA 21-738.

Studies reviewed within this submission: None

Studies not reviewed within this submission: N/A

3.2   PHARMACOLOGY:

3.2.1   Brief summary: The primary pharmacodynamic target(s) of KTZ like other imidazole antifungals is the cell membrane in the fungus, which is structurally disformed and made dysfunctional. KTZ inhibits cytochrome P450 enzyme lanosterol 14α-demethylase, which is responsible for the oxidative removal of C-14 methyl group from lanosterol or 24-methylene-dihydrolanosterol. These sterols are the precursors of the critical membrane component ergosterol. Lanosterol and its analog methyl sterols due to their protruding methyl groups do not properly fit in the mosaic of membrane causing it to become permeable to protons and eventual burst (1). The fungal mitochondria also contain high concentration of ergosterol, and its deficiency may also lead to dysfunctional enzymes. In addition, depletion of ergosterol may also interfere with the regulation of chitin synthesis, another component of the cell wall (2).

The low dose effects of KTZ mentioned above are essentially fungistatic in nature not fungicidal because the inhibition will be effective only when the organism is growing and dividing. However, the cumulative concentration of KTZ attainable in topical therapy may be fungicidal as well (3). This action may include direct action with the membrane lipids. The accumulated sterols may disrupt the close packing of acyl chains of phospholipids, impairing the functions of membrane bound ATPase and enzymes of the electron transport system (2).

Because some imidazole antifungals are also effective against certain gram +ve and anerobic bacteria and protozoans (e.g. *Staphylococcus aureus, Streptococcus faecalis, Bacillus fragilis, and Leishmania*) which do not have ergosterol, other primary pharmacodynamic mechanisms also appear to be involved (4).

KTZ at low topical concentrations is relatively specific in inhibiting the fungal lanosterol demethylase as opposed to the same enzyme from rat

liver. Nevertheless, at higher oral doses, a number of other animal cytochrome P450 enzymes, particularly those involved in the interconversion of steroid hormones are also inhibited. For instance, the concentration of KTZ required to inhibit the cholesterol synthesis in human fibroblasts was 140 times greater than required to inhibit the ergosterol synthesis in yeast (5). Additional examples are the rate-limiting steps in the production of glucocorticoids and sex steroids. This property has been used for the treatment of androgen-dependent diseases. For instance, prostate and breast cancers where reduced steroid levels are desirable. KTZ has also been used in the treatment of adrenal cancer when the surgical therapy is impractical or unsuccessful because of metastases (6). It has also been used in the treatment of yeast keratitis and endophthalmitis (2).

It is believed that *Malassezia furfur* is associated with the inflammatory components (erythema, burning, and edema) of seborrheic dermatitis. The susceptible host is presumed to react against this yeast with an immune response which include the formation of inflammatory leukotrienes. The secondary pharmacodynamic (anti-inflammatory) action of KTZ is the inhibition of 5-lipoxygenase involved in the conversion of arachidonic acid to leukotriene B4 (7). A number of *in vivo* and *in vitro* studies have supported this hypothesis. For instance, the topical application of 2% KTZ blocked the arachidonic acid-induced ear edema in a mouse model dependent upon 5-lipoxygenase activity (8). The sponsor suggests that the combined primary and secondary pharmacodynamic actions of KTZ would be effective in the treatment of seborrheic dermatitis.

3.2.4 Safety pharmacology:

Neurological effects: Not investigated

Cardiovascular effects: Following an intravenous dose of 5mg KTZ/kg to dogs, the duration of action potential and the effective refractory time in the isolated Purkinje fibers and papillary muscle were slightly increased. In the anesthetized dogs receiving intravenous doses of 5-10mg KTZ/kg, no biologically significant changes in the cardiac function were observed.

Pulmonary effects: Not investigated

Renal effects: Not investigated

Gastrointestinal effects: Not investigated

Abuse liability: Not known

3.2.5   Pharmacodynamic drug interactions: The hepatic microsomal enzyme inducer drugs (e.g. rifampin, isoniazid) enhance the metabolic clearance of KTZ, reducing its plasma concentration by more than half. On the other hand, KTZ raises the plasma concentration of drugs metabolized by cytochrome P450 enzyme CYP3A4 (e.g. cyclosporine, midazolam, triazolam, indinavir, and phenytoin) (2). However, because of poor (< 1%) dermal absorption of KTZ in humans, the systemic concentrations required for such undesirable interactions will be hard to achieve with the topical formulations.

3.3   PHARMACOKINETICS/TOXICOKINETICS

3.3.1   Brief summary: In humans as well in animals, the absorption of KTZ from the topical formulations is less than one percent. In fact in several studies, the plasma drug concentrations were below the detection limit of 2ng/mL. Because of this limitation, other pharmacokinetic parameters (distribution, metabolism, and excretion) using the dermal route are hard to determine. The information about these parameters is mostly drawn from the oral, peritoneal, and intravenous studies in rats and dogs. In rats receiving oral doses, the rates of metabolism and elimination were relatively low in females. In rodents and dogs, KTZ is metabolized into a large number (>22) of metabolites. The metabolite N-deacetyl ketoconazole (DAKC) is considered to be the major toxicant in animals. It is suggested that the abundant binding of KTZ to liver microsomes could cause auto-inhibition of its metabolism. KTZ in humans is extensively metabolized, however, the metabolic pathways in humans are not clearly understood.

3.3.3 Absorption: In animals as well as in humans, a limited amount (<1%) of KTZ is topically absorbed. In fact, in most studies the plasma drug levels remained below the detection limit of 2ng/mL.

In a single oral dose study, the absorption of 10mg/kg ^{3}H-KTZ in male rats, male guinea pigs, male rabbits, and female dogs was investigated. At two hours post-dose, the mean plasma levels of the parent drug varied from 0.9 in rabbits to 12.9μg/mL in rats. The plasma drug concentration decreased rapidly with the elimination $t_{1/2}$ varying from 0.70 hour in guinea pigs to 2.76 hour in dogs (9).

The percutaneous absorption of foam and cream formulations using the dermatomed human cadaver skin was investigated. In the first study (4-6mg KTZ/cm^2); at 24 hours post-dose less than 1% of the applied dose was found in the receptor fluid. In the second experiment, at 24 hours post-application, only 0.2% was found in the receptor fluid, a major portion was present in the surface wash, followed by epidermis and dermis.

The oral excretion data indicated that in rats KTZ is almost completely absorbed but is subject to a large first pass effect (16). The absorption in dogs is poor because over 55% of the fecal radioactivity was due to the intact drug (17). In a human oral study, 35-75% of KTZ was absorbed (9).

In a 4-week human bioavailability study where patients with moderate to severe seborrheic dermatitis received daily topical applications of Extina™ (Ketoconazole Foam, 2%) equivalent to 120mg of KTZ, the average plasma drug level was 6ng/mL.

3.3.4   Distribution: It is logical to assume that the distribution patterns of the topically and orally absorbed KTZ are similar.

The tissue distribution of KTZ following its oral administration had been extensively studied in rats. These investigations were also extended to pregnant guinea pigs and lactating dogs. Male and female rats after receiving an oral dose of 20mg^{3}H-KTZ/kg were sacrificed at various post-dose time points. The amounts of radioactivity (parent drug plus metabolites) in males/females (µg-equivalent/g) were found in the following decreasing order: liver 125/124, adrenals 93/156, and pituitary 43/51. These levels were much higher than the mean plasma levels of 31/36µg/mL. The residual levels of drug (4-11µg-equivalent/g) found in the skin persisted for 24 hours (9).

The distribution patters in male and female rats were different. Whereas in males, the highest amount of radioactivity was present in the liver, in females this amount was found in the adrenals. This difference was attributed to a rapid clearance of KTZ from the GI-tract and saturation in males (4 hours) than females (8 hours). The extended liver saturation in females indicated a slow metabolism resulting into enhanced tissue distribution and slow elimination (9).

Following the escalating intravenous doses of KTZ in rats, a non-linear kinetics in AUC, CL, and Vd was observed (10). A similar pattern of disproportionate increase in AUC was also observed in humans following oral doses of 100-800mg. This nonlinearity indicated a saturable hepatic metabolism (11).

3.3.5   Metabolism: The oral studies in rats, mice, and dogs revealed that KTZ was extensively metabolized to a large number (>22) of compounds, with hepatic microsomal enzymes playing the major role in its biotransformation. The suggested metabolic pathways include oxidation, cleavage, degradation, and scission of imidazole and piperazine rings, *O*-dealkylation, and aromatic hydroxylation (11). In mice, N-deacetyl ketoconazole (DAKC) is considered to be the major metabolite (12). In rat hepatic microsomes DAKC is further metabolized by a flavin-containing monoxygenase; and in a microsomal assay, the rate of disappearance of

KTZ was almost equal to the rate of appearance of DAKC (13). An oral study in dogs indicated an extensive conversion to a number of inactive metabolites (14). In humans, KTZ is extensively metabolized, however, the metabolic pathways are not clearly understood (9, 15).

In rats, the disposition of KTZ was dose and sex-dependent (18). After a single intravenous dose (10, 20, 40mg/kg), the plasma drug profiles in both sexes exhibited an initial rapid decline, followed by a zero order decline and eventually a first-order elimination phase. In males, the overall rate of elimination was 3-5 times higher. A four-fold increase in dose resulted in 9- and 17-fold increase in AUC of males and females, respectively. The dose-independent terminal half-life was also slightly higher in females (2.14 hours in females, 1.17 hours in males). In both sexes, no intact drug was excreted in the urine, and less than 1% was found in the bile. The dose-dependent disposition of KTZ is attributed to the saturation of metabolizing enzymes. It is suggested that these enzymes are under the influence of androgens, since the ability of males to eliminate KTZ was reduced after castration and in females it was enhanced by testosterone treatment.

In dogs during the chronic drug administration, the plasma drug levels remained stable, reflecting the absence of hepatic microsomal enzyme induction. A similar pattern was observed in rats except at the near toxic dose levels of 80-160mg/kg/day (20)

The oral studies in rats indicated that at higher dose level, KTZ and its metabolites were mainly concentrated in the liver, not in the plasma. Approximately 90% of KTZ was specifically bound to the liver microsomal fraction, suggesting that the drug may cause potent auto-inhibition of its own mixed-function oxidase metabolism.

3.3.6 **Excretion:** The drug elimination was investigated in rats and dogs via the oral and intravenous routes. As in case of metabolism, elimination was also dose and sex-dependent. At 24 hour post-dose following a single oral dose of 20mg/kg, male and female rats excreted 90 and 78% of the orally administered KTZ, respectively. At 4 days post-dose, both sexes excreted the same amount (95%), but the urinary elimination of KTZ in males (17%) was much greater than females (5%). In both sexes, whereas only traces (0.1%) of the parent drug were found in the urine, approximately 5% of the administered dose was excreted in the feces (9).

Following an oral dose in rats, 95% of the radioactivity was excreted in 4 days (80% in the feces and 15% in the urine). The intact drug in the urine and feces accounted for 0.1 and 4-6% of the administered dose, respectively. The rest of the activity was due to metabolites. In another oral rat study (20mg/kg), at 24 hours post-dose 60% of the radioactivity

was found in the bile, the intact drug accounted only for 0.3% of the administered dose (9).

In male rats treated intravenously with 5mg/kg of ^{3}H-KTZ, within 7 days more than 80% and 16% of the administered dose was excreted in the feces and urine, respectively. However, whereas the urine excretion was complete in two days, fecal elimination continued after day 7 (16).

In two female Beagle dogs following an oral dose of 10mg ^{3}H-KTZ, 92% of the administered radioactivity was recovered within 7 days (83% in the feces, and 9% in the urine). In contrast to rat study, approximately 70% of the fecal radioactivity was due to intact drug, possibly due to poor absorption (9).

As in animals, the elimination of KTZ in humans is also dose-dependent. With dose and the duration of treatment, the terminal $t_{1/2}$ for KTZ in humans varies from 1.5 to 6 hours (4).

3.3.6   Pharmacokinetic drug interactions: N/A

3.3.10   Tables and figures to include comparative TK summary: N/A

3.4   TOXICOLOGY

3.4.1   Overall toxicology summary: The toxicity potential of KTZ has been investigated in a wide spectrum of animal studies conducted in multiple species via different routes of administration. However, the proposed 2% KTZ foam formulation was not tested in any of these studies.

Absolutely, no systemic or local toxicity was observed in 4-week dermal studies employing intact and abraded skin sites on rabbits (40mg KTZ/kg/day) and dogs (80mg/kg/day). The plasma drug levels in both cases were below the detection limit of 2ng/mL. These doses were established as dermal NOAELs in the respective species.

In a 4-week clinical study where patients with moderate to severe seborrheic dermatitis received daily topical applications of 120mg KTZ from the proposed 2% foam formulation, the average plasma drug level was 6ng/mL.

In bacterial reverse mutation assay, ketoconazole did not express any mutagenic potential. In three *in vivo* assays (sister chromatid exchange in humans, dominant lethal and micronucleus tests in mice), ketoconazole did not exhibit any clastogenic potential or induced sister chromatid exchange. At the oral dose levels of 75-80mg/kg/day, ketoconazole damaged the reproductive performance in female (decreased pregnancy

and implantation rates) and male (increased abnormal sperms and decreased sperm mobility) rats.

The oral carcinogenicity studies in mice (18 months) and rats (24 months) at dose levels of 5, 20 or 80mg/kg/day, did not indicate any drug-related changes in the survival rate, and the incidence and type of tumors.

In a segment II oral rat study, KTZ at dose level of 80mg/kg/day caused teratogenic effects including oligodactyly and syndactyly. However, it was suggested that these effects might also be partly attributed to maternal toxicity, which was also observed at this dose level.

In reproductive performance studies in rats and dogs, a significant decrease in the serum testosterone levels, decreased sperm mobility, increase in the number of abnormal sperms, focal tubular atrophy and hyperplasia of Leydig cells, and vacuolation of zona fasciculata were observed in males at dose levels ranging from 25 to 75 mg KTZ/kg/day. The major effects in females included prolonged gestation period, and the reduced litter sizes. The NOEL for maternal toxicity was considered to be 10mg/kg.

The data generated from the *in vivo* and *in vitro* animal studies has indicated that the metabolite DAKC was linked to hepatotoxicity, induction of phospholipidosis, and auto-inhibition of microsomal metabolism of KTZ. It is proposed that

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In a nutshell, because of limited dermal absorption and short elimination $t_{1/2}$ for KTZ, the systemic toxicity due to 2% KTZ foam formulation will be minimal. In the oral reproductive and developmental toxicity studies, KTZ was evaluated as teratogenic and embryotoxic. And based on these data, pregnancy category C was assigned to its approved tablet, cream and shampoo formulations.

General toxicology:

In a 4-week topical study, the intact and abraded skin sites on the back of beagle dogs received daily applications of 80mgKTZ/kg/day from a 2% cream formulation. Absolutely, no dermal reactions or systemic toxicity were observed during or after the treatment. The plasma drug levels were below the detection limit of 2ng/mL. The data indicated that the topically applied KTZ was not absorbed to a measurable strength (19).

In a 30-day topical study in NZW rabbits, the intact and abraded skin sites on the back received daily applications of 2g placebo cream, 0.5g (10mg KTZ), 1.0g (20mg KTZ) or 2.0g (40mg KTZ) of 2% KTZ cream. No changes in body weights or any clinical signs of toxicity were observed throughout the study period. A slight dermal irritation was observed in all animals including the control (19).

In a subchronic oral study, two groups of male (n=30 and 39) Sprague-Dawley rats further divided into three equal number of subgroups received 0, 25, or 75mg KTZ/kg/day. The two main groups were treated for 8 and 13 weeks, respectively. A dose related increase in adrenal weight was observed. Histopathological examination revealed an increase incidence of focal tubular atrophy and hyperplasia of Leydig cells, and hyperplasia and hypertrophy of the zona glomerulosa. A reduction in the plasma testosterone was also recorded (23).

In a 4-week oral male beagle dog study, two groups of animals received 0 or 25mg KTZ/kg/day. From each group, two animals were kept for 4 weeks of recovery period. A transient decrease in food consumption was observed during the first two weeks of treatment. A slight decrease in plasma testosterone with simultaneous increase in plasma progesterone levels was recorded. No changes in organ weight were observed. Histopathological examination indicated a marked increase in the incidence of minimal focal tubular degeneration and atrophy of the testes (24).

In an acute eye irritation study in NZW rabbits, a single application of 0.1mL of 2% KTZ cream did not cause any ocular irritation (19).

In one-month oral male cat study (30mg/kg/day), animals exhibited dry hair coats, and reduction in body weights by 150-550 grams. A decrease (43%) in serum alkaline phosphatase was observed. The serum progesterone concentration increased by 34%, while the serum testosterone level decreased by 66 percent (21).

Genetic toxicology:

In Ames *Salmonella typhimurium* assay, KTZ tested non-mutagenic with or without rat liver microsomal activation system (22).

The *in vitro* chromosomal aberration and *in vivo* sister chromatid exchange (SCE) assays were conducted using human lymphocytes. For the first study, the cultures were incubated with 3-50μg KTZ/mL for 48 hours. An increase in gaps and chromatid breaks was observed at 6μg/mL and above. For the second study, lymphocytes were collected from a 10-year male treated with 100mg KTZ/day for 211 days, and a 44-year female treated

with 200mg KTZ/day for 509 days. The cultures were prepared and tested before, after and during the treatment. When compared with the pretreatment values, the treatment with drug did not increase the number of SCEs in the lymphocyte (22).

Two oral dominant lethal assays were conducted in Swiss albino mice. In the first study, male mice treated with 20, 80 or 320mg KTZ/kg were mated with untreated females. In the second test, treated females (20, 80 or 160/320mg/kg) were mated with the untreated males. KTZ did not induce dominant lethal mutations in the male or female germ cells at any dose level.

In a micronucleus assay (20, 40 or 80mg/kg), KTZ did not increase the number of normochromatic or polychromatic cells in the male mice.

Carcinogenicity: Two dietary admix carcinogenicity studies (50 animals/sex) were conducted in mice (18 months) and rats (24 months) at dose levels of 5, 20 or 80 mg KTZ/kg/day. In both studies, no drug-related effects on the survival, body weights, food consumption, and incidence and type of tumors were observed.

Reproductive toxicology:

In the general fertility and reproductive performance study, two groups (n=30 and 39) of Sprague-Dawley male rats were treated with oral KTZ for 8 and 13 weeks, respectively. Each group further divided in three subgroups received 0, 25 or 75mg KTZ/kg/day. The entire 69 drug treated males were mated for a maximum of 3 weeks with the untreated females. The treatment of males during the mating period continued. After pairing the blood samples were drawn for the determination of plasma testosterone level. Thereafter in the sacrificed males, testicular and epididymal sperm count, epididymal spermatazoa morphology and motility were determined. The organ weights for testes, epididymides and adrenals were determined, and these organs were also subjected to histopathological examination. On day 20, the uterine content and fetuses were removed for examination (23).

At the high-dose level, reduced (-19 to –26%) spermatozoa mobility associated with the reduced plasma testosterone levels (-41 to -68%) were observed. In addition, an increase (+74 to +81%) in the number of abnormal spermatozoa based on an increased incidence (+74 to +223%) of detached sperm heads was recorded. The changes in sperms caused a reduction (-30 to –34%) in male fertility, only ~66% of the high-dose females became pregnant.

A dose related increase in the adrenal weights was recorded in all the KTZ treated males. The microscopic lesions in the testes and adrenals included increased incidence of focal tubular atrophy and hyperplasia of Leydig cells, and hypertrophy of zona glomerulosa resulting in reduced or disappeared zona fasciculata. The severity of the histopathological lesions was directly related to the dose and the duration of treatment. No changes were observed in females. No external fetal abnormalities were observed.

In another segment I study, two groups of 4-5 male beagle dogs received 0 or 25mg KTZ/kg/day for 4 weeks. Two animals from each group were subjected to a recovery period of 4 weeks. The clinical pathology parameters (ASAT, ALT, and ALP), plasma testosterone and progesterone levels, and the motility, count and morphology of sperms were determined (24).

The drug treatment caused a decrease in food consumption and body weights in weeks 1-2, decrease in sperm motility in week 1, an increase in the number of abnormal sperms in week 2, and a decrease in sperm count in week 4. The plasma progesterone and testosterone levels were increased and decreased, respectively. KTZ also induced minimal tubular degeneration and atrophy of testes. None of the above mentioned adverse effects were observed during the recovery period.

Following the intraperitoneal injections of 1, 4 or 10mg KTZ every 12 hours for two weeks, the effect of drug on the serum testosterone level in five groups (n=8) of male Wistar rats was investigated. At one hour post-dose in the 1mg group, the testosterone level dropped by 20 percent, however, after 12 hours, the level recovered to 50 percent of the control value. In the mid-dose group, the level was minimal at 12 hour, but thereafter remained undetectable throughout the study period. In the high-dose group, no testosterone was detected throughout the post-dose period. In addition, half the rats died, the rest exhibited diarrhea, lethargy and emancipation. A dose greater than 4mg completely inhibited the testosterone surge induced by the administration of a potent lutenizing releasing hormone agonist (6-leucine 1-9 nonapeptide Irh) (25).

From another male Wistar rat study, it was learned that the changes in the sperm motility and steroidgenesis were related to the presence of KTZ in the epididymal and seminal fluids. A single oral dose of 300mg/kg induced immobilization of spermatozoa in the cauda epididymis at 8 and 24 hours post-dose, when the organ concentration of KTZ was at the peak. The sperm motility became normal at 48 hours when the local drug concentration dropped below the critical level (26).

It is suggested that KTZ inhibition of testicular steroidgenesis is related to its effect on the 17, 20-lyase (a microsomal cytochrome P-450 enzyme) -

dependent conversion of 17α hydroxyprogesterone to testosterone. This hypothesis is supported by the fact that in patients receiving oral doses of KTZ, an increase in the plasma levels of 17α hydroxyprogesterone was observed (27, 28).

In a segment II oral rat study, KTZ at dose level of 80mg/kg/day caused teratogenic effects including oligodactyly and syndactyly. However, it was suggested that these effects might also be partly attributed to maternal toxicity, which was also observed at this dose level.

In two segment II studies, KTZ was orally administered to rats (10, 20 or 40mg/kg/day) and mice (10, 25 or 50mg/kg/day) on gestation days 6 through 21 and 6 through 18, respectively (29).

No maternal toxicity or maternal deaths were observed. A high incidence of resorptions, increased number of stillbirths, and delayed parturition were observed in the mid- and high-dose mice. All the high-dose female rats failed to deliver naturally, and their cesarean examinations (3 days after the due date) showed well-formed live and dead fetuses as well as a high number of resorption sites.

Birth weights of pups were significantly reduced in the mid-dose rats and the high-dose level mice. The late descent of testes and vaginal opening were observed in many pups of both the species.

Eight to nine weeks old mid- and high-dose rat pups had difficulty in drinking and eating due to malocclusion of incisors.

It was inferred that KTZ causes intrauterine growth retardation, and inversely affects the parturition and postnatal development in both the species, but more so in rats.

In a segment III oral study in pregnant rats, the effects of KTZ (10, 40 or 160mg/kg/day) from day 16 of gestation through 3-weeks of the lactation period were investigated. The mid- and high-dose females exhibited a 10% increase in the mortality rate, a substantial decrease in the pregnancy rate, maternal weight gain and food consumption, longer gestation period, greater number of dead fetuses, and decreased litter size. Also, the pups in both groups had significantly decreased body weights and survival rate. The NOEL for maternal and fetal toxicity was considered to be 10mg/kg.

Special toxicology: No studies were conducted with the proposed formulation.

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3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Over the last two decades, the safety of ketoconazole (KTZ) has been widely evaluated in a large number of studies in multiple animal species. However, most of the pharmacokinetic studies were conducted using the oral route. Reason, in animals the dermal absorption of KTZ is minimal, and in most cases the plasma drug level remained below the detection limit of 2ng/mL. As a result, a limited amount of animal pharmacokinetic data for topical KTZ is available. However, the pharmacokinetic and pharmacodynamic behavior of KTZ irrespective of its route of administration should be the same.

The teratogenic damage (syndactyly and oligodactyly) in rats occurred at an oral dose level of 80mg/kg/day (~30 times the expected human dose in mg/kg, and ~5 times in mg/m^2) and above.

In two rodent oral carcinogenicity studies (5, 20, and 80mg/kg/day), no drug related changes in tumor type and number were recorded.

In 4-week dermal studies using abraded and intact sites in rabbits (40mg/kg/day) and dogs (80mg/kg/day), absolutely no systemic or local toxicity was observed. The plasma drug levels in both cases were below the detection limit. The dose levels of 40 and 80mg/kg (5-16 times the expected topical human dose in mg/m^2) were established as dermal NOAELs (no observed adverse effects level) for rabbit and dog, respectively.

In a 4-week clinical study where patients with moderate to severe seborrheic dermatitis received daily topical applications of 120mg of KTZ from the proposed 2% foam formulation, the average plasma drug level was 6ng/mL.

The duration of non-clinical/clinical treatment of 4 weeks, and pharmacokinetic data such as elimination half-life in dog and human are similar. Therefore, dog is a suitable model for risk comparison.

The data provided by the sponsor indicated that during the treatment, a patient received approximately 8 grams (equivalent to 160mg KTZ) of the foam formulation per day. A hypothetical absorption of 100 percent will provide a concentration of 2.7mg KTZ/kg/day (~100mg/m^2). Using NOAEL in dog, the margin of safety (w/w) is ~30 times of the expected human dose, in terms of body surface area it will be ~16 times.

During two decades of their global use, the approved dermal products of KTZ (2% cream and shampoo) have not caused any serious systemic and or local adverse effects.

A concern about the presence of toxic alkaloid brucine sulfate in denatured alcohol ——————— component of the foam formulation was raised ——————— is an approved inactive ingredient at the topical level of 60.16 percent. It has been used in a few topical prescription drug products (e.g. in Retin-A at 55% concentration). The proposed formulation contains ——————— of ——————— at the maximum.

b(4)

Strychnine and brucine, two structurally related alkaloids are extracted from Strychnus nux vomica L. (poison-nut tree) and Strychnus ignatii Berg. These compounds have been used as analeptic, analgesic and anti-inflammatory agents in Chinese herbal medicines. In the past, brucine sulfate had also been used in the veterinary medicine in equal parts with strychnine in tonic and stimulant formulations. Commercially, brucine has been used to denature alcohol and oils. Toxicity of brucine occurs through work place inhalation (irritation to eyes, nose and throat) and

ingestion of pharmaceuticals containing this compound. It is a potent inducer of hepatic drug metabolizing enzymes in rat. Brucine tested non-mutagenic in Ames test at the highest dose level of 6,666 µg/mL. The acute toxicity data of brucine is given below (Cf. Registry of Toxic Effects of Chemical Substances 1997).

Lowest published lethal dose(mg/kg body weight)
Rabbit intravenous: 30
Guinea pig intravenous: 120
Dog intravenous: 8
Pigeon subcutaneous: 58

Lethal dose (mg/kg body weight) 50percent KILL
Rat intraperitoneal: 91
Mouse: *intraperitoneal*: 62
          intravenous: 12
          oral: 150
          subcutaneous: 60

Taking into account the lowest intravenous lethal dose of 8mg brucine/kg in dog, the equivalent dose in a human subject will be 480milligrams. Each 51 grams tube of Extina contains a maximum of ———brucine. Assuming intravenous route of administration, it will take 114 tubes or 5.8kg foam formulation/day to cause a similar lethal effect in patients. An impossible goal to achieve.

b(4)

Based on the maximum reported concentration of ———Brucine in 8 grams of Extina, a 60-kg person (assuming 100% absorption) will receive 0.01mg/kg of this compound. The lowest lethal dose of brucine in dog is 8mg/kg. The margin of safety in terms of mg/kg will be 800 times the expected human topical dose; in terms of mg/m^2 it will be 432 times. However, the absorption of comparatively much more lipophilic KTZ never exceeded 1%, therefore, it is expected that the dermal absorption of much polar brucine sulfate **salt** will be even lower. So in real terms, the actual margin of safety will be at least 80, 000 (w/w) to 43, 200 times (mg/m^2). The chances of brucine sulfate causing any systemic or local toxicity in patients are negligible.

Unresolved toxicology issues (if any): None

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

Suggested labeling:

b(4)

b(5)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence
Yes ___ No ___

3.7.   **APPENDIX/ATTACHMENTS**

Appears This Way
On Original

Date: 03-12-04
Reviewer: Kumar D. Mainigi
NDA Number: 21-738
Drug Name: Extina™ (Ketoconazole Foam 2%)
CAS Number: 65277-42-1
Drug Class: Antifungal
Indication: Seborrheic dermatitis
Route of Administration: Topical
Date CDER Received: 01-26-04
User Fee Date:
Date of Draft Review: 15 June o4
Sponsor: Connetics Corporation, South Haven, MI

<u>**Fileability:**</u>
On initial overview of the NDA application: Filable

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner to allow a substantive review to be completed?   Yes

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review?   Yes

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed?   Yes

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?   Yes

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product <u>or</u> to explain why such repetition should not be required?   Yes

(6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?
            Yes
(7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor?   N/A

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor <u>submitted</u> a rationale to justify the alternative route?
            Yes
(9) Has the Sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?
            N/A
(10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics?   N/A

(11)   Has the Sponsor <u>submitted</u> a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?   N/A

(12)   From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.
                                                        Yes
(13)   If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify:
                                                        None
(14)   Issues that should not be conveyed to the Sponsor: N/A

_Kumar D. Mainigi_____
Pharmacology Reviewer

_Paul Brown_____
Pharmacology Supervisor

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