CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-385

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-385	Submission Date: 10/9/2003
Brand Name	ERTACZO™ Cream
Generic Name	Sertaconazole nitrate
Reviewer	Lei Zhang, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm. D.
OCPB Division	DPE III
ORM Division	DDDDP (HFD-540)
Applicant	Mylan Pharmaceuticals Inc.
Relevant IND	IND 50,726
Type of Submission; Code	505 (b)(1); Resubmission (Class I) Response to Agency's July 26, 2002 Approvable Letter
Formulation; Strength(s)	Cream 2% (2g, 15g, 30g)
Indication	[redacted]

NDA 21-385 Resubmission

Background

An approvable letter was sent to the sponsor from the Agency in July 2002 regarding NDA 21-385. From the Clinical Pharmacology and Biopharmaceutics aspects, the pivotal PK study in the application was found to be inadequate for the assessment of in vivo bioavailability in that it used too small number of patients (5 tinea pedis) and some patients were not under maximal use conditions. The following comments were conveyed to the sponsor in the letter: "The major pharmacokinetic study for this application is inadequate for the assessment of in vivo bioavailability. [redacted]

In this resubmission, no new data was provided. The sponsor requested a clarification regarding the Agency's request for the [redacted]

From the PK study SERT-9758, only 5 patients had interdigital tinea pedis (the proposed indication) (See Table 1). Among them, only 2 patients had diseased areas > 100 cm^2 (closer to maximal possible diseased areas). Because of cracking, bleeding and occlusive nature of tinea pedis, vascular absorption of drug is possible. The in vivo bioavailability in tinea pedis will be different from that in tinea cruris. Therefore, the PK data from patients with tinea cruris could not be extrapolated appropriately to determine in vivo bioavailability in patients with tinea pedis.

Table 1: Clinical Diagnosis

Patient	Type of Infection	KOH Wet Mount	Fungal Culture	Type of dermatophyte(s)	Lesion Area (cm^2)
001	Interdigital Tinea Pedis	Positive	Positive	*T. rubrum*	
002	Tinea Cruris	Positive	Positive	*T. rubrum*	
003	Interdigital Tinea Pedis	Positive	Positive	*T. rubrum*	
004	Interdigital Tinea Pedis	Positive	Positive	*T. rubrum*	
005	Interdigital Tinea Pedis	Positive	positive	*T. rubrum*	
006	Tinea Cruris	Positive	Positive	*T. rubrum*	
007	Interdigital Tinea Pedis	Positive	Positive	*T. rubrum*	
008	Tinea Cruris	Positive	Positive	*T. rubrum*	
009	Tinea Cruris	Positive	Positive	*T. rubrum*	
010	Tinea Cruris	Positive	Negative	NA	

Comments

The sponsor's response to Biopharmceutics' Comments in the AE letter and proposed revised draft labeling have been reviewed. Please convey the following comments to the sponsor.

1. The response did not fulfill the in vivo bioavailability requirement under 21CFR320.
   a) The data from Study SERT-9758 still does not meet the requirement to assess in vivo bioavailability of sertaconazole for the indication proposed.
      Due to:
      - Small number of subjects (5 out of 10) that had the qualifying interdigital tinea pedis infection
      - Small number of subjects (2 out of 5) that may qualify for maximal use conditions for the proposed indication
      - Data from tinea cruris could not be extrapolated for tinea pedis because disease location can alter the permeation characteristics of diseased skin.
   b) There is no additional information provided to confirm the negligible exposure of sertaconazole in patients with interdigital tinea pedis.

2. Please delete the results from [redacted] section of the labeling and keep this section as previously recommended in the approvable letter (dated July 26, 2002) because [redacted]

Recommendation

The Clinical Pharmacology and Biopharmaceutics response in this NDA resubmission is not acceptable. [redacted]

[redacted] The "Clinical Pharmacology" section in the revised labeling (in this submission) is recommended to be kept as previously recommended in the approvable letter (dated July 26, 2002).

Lei Zhang, Ph.D.
Division of Pharmaceutical Evaluation III

Concurrence:

E. Dennis Bashaw, Pharm. D.
Team Leader, Division of Pharmaceutical Evaluation III

CC: NDA 21-385; HFD-540/Div File; HFD-540/RPM/Cross;
HFD-880 (Lazor/Selen/Bashaw/L.Zhang)

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/s/

Lei Zhang
11/5/03 01:47:06 PM
BIOPHARMACEUTICS

Dennis Bashaw
11/5/03 04:36:45 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-385	Submission Date: 10/9/2003
Brand Name	ERTACZO™ Cream
Generic Name	Sertaconazole nitrate
Reviewer	Lei Zhang, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm. D.
OCPB Division	DPE III
OND Division	DDDDP (HFD-540)
Applicant	Mylan Pharmaceuticals Inc.
Relevant IND	IND 50,726
Type of Submission; Code	505 (b)(1); Resubmission (Class I) Response to Agency's July 26, 2002 Approvable Letter
Formulation; Strength(s)	Cream 2% (2g, 15g, 30g)
Indication	[redacted]

NDA 21-385 Resubmission
Addendum to Review

An approvable letter was sent to the sponsor from the Agency in July 2002 regarding NDA 21-385. From the Clinical Pharmacology and Biopharmaceutics point of view, the pivotal PK study in the application was inadequate for the assessment of in vivo bioavailability. The reasons being that the study population was mixed between tinea pedis and tinea cruris, and that the tinea pedis patients few in number (N=5) and they were not all under so called "maximal use" conditions.

This application was re-submitted on Oct 9, 2003. The sponsor chose not to do a new pk study but to re-submit the old data and to cite the large surface area involvement with the included tinea cruris patients and ask us to reconsider the Agency's request for conducting a new PK study. Our review at this time (signed off in DFS on 11/5/03) re-affirmed our contention that a larger trial in tinea pedis patients was needed.

Subsequent to a conversation with the sponsor the Division of Pharmaceutical Evaluation-III undertook a search of the administrative record of this NDA. In the notes from previous meetings going back to the end of phase 2 meeting in 1997, it was revealed that the very approach the sponsor pursued, using a mixed tinea population, was in fact recommended by the Agency to the sponsor [see comments excerpted from mintues below].

EOP2 Meeting 6/23/97

Biopharmaceutics:
Agency: The Agency recommended the following:
1. [redacted] For example, tinea corporis or tinea versicolor can involve much greater

body surface area, a PK study for tinea corporis or tinea versicolor may support the indication of interdigital tinea pedis.(emphasis added).
2. In general, PK studies are to be conducted in patients with severe disease conditions in large surface area of the skin consistent with labeling. If the drug product can be used with occlusion, the study should take this into consideration. The purpose is to examine the possible maximum systemic exposure. We would like to see results from a single topical application as well as from multiple applications.
3. Scarified skin may not mimic the diseased skin in that the former usually affects only the top layer of the skin.

This approach was later affirmed both in a protocol review in 1998 and at the pre-NDA meeting in Oct. 2000. In light of the FDA's initial encouragement to the sponsor to pursue the route they did, the Agency cannot now, after affirming this route throughout the previous meetings and reviews, disavow it. Therefore, upon re-consideration of the data and the administrative record, the sponsor has fulfilled the in vivo bioavailability requirement under 21CFR320 and the [redacted] proposed in the original review by Dr. Lee and confirmed by Dr. Zhang in her review is removed.

Lei Zhang, Ph.D.
Division of Pharmaceutical Evaluation III

Concurrence:

E. Dennis Bashaw, Pharm. D.
Team Leader, Division of Pharmaceutical Evaluation III

CC: NDA 21-385; HFD-540/Div File; HFD-540/RPM/Cross;
HFD-880 (Lazor/Selen/Bashaw/L.Zhang)

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/s/

Lei Zhang
12/9/03 12:57:04 PM
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Dennis Bashaw
12/9/03 01:00:16 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: **21-385**	Submission Date(s): **09/28/01**
Brand Name	**To be determined**
Generic Name	**sertaconazole nitrate cream, 2%**
Reviewer	**Jang-Ik Lee, Pharm.D., Ph.D.**
Team Leader	**E. Dennis Bashaw, Pharm.D.**
OCPB Division	**DPE III (HFD-880)**
OND division	**ODE V (HFD-540)**
Sponsor	**Mylan Pharmaceuticals Inc.**
Relevant IND(s)	**50,726**
Submission Type; Code	**NME; 1S**
Formulation; Strength(s)	**cream 2% (2 g, 15 g, 30 g)**
Indication	

1. EXECUTIVE SUMMARY

Sertaconazole is an imidazole antifungal agent with a broad spectrum of action against pathogens that cause skin and mucosal infections. Sertaconazole is being marketed in 48 countries other than the United States for the treatment of superficial infection of yeasts or dermatophytes as various formulations including cream. Ferrer International initially developed this product in Spain. Mylan Pharmaceuticals introduces the product in the United States under a licensing agreement with the innovator. In this original NDA submission, the sponsor pursues an approval of sertaconazole nitrate cream 2%

There is a total of 10 pharmacokinetic study reports consisting of 6 volumes in this NDA (Table I). Among them, Study SERT-9758 conducted in a small number of patients with tinea pedis and tinea cruris contains information on the systemic absorption of sertaconazole through diseased skin from 2% cream. Study PAZ 3018/295 conducted in healthy volunteers are only complementary to Study SERT-9758 because the extent of sertaconazole delivery to and penetration through healthy skin cannot be the same as that to and through diseased skin (tinea pedis). Study CL-PH-1 and Study THE/SER/91003 are not acceptable since the analytical methods used are not sensitive enough to measure sertaconazole concentrations around estimated no-observable-effect-level (NOEL) and were not satisfactorily validated.

The degree of systemic absorption and skin uptake are not adequately characterized to support the dosage and administration of sertaconazole nitrate cream 2% proposed by the sponsor. Based on the limited data submitted in this NDA, the systemic absorption of sertaconazole from 2% cream through the diseased and surrounding skin of patients with interdigital tinea pedis appears to be negligible. The number of study patients recruited in the pivotal pharmacokinetic study (5 tinea pedis), even with reinforcement by the addition of 4 patients in tinea cruris, is not sufficient to draw a firm conclusion and, therefore, additional data are required.

1.1. Recommendation

The pivotal pharmacokinetic study, as conducted in this application, is inadequate for the assessment of in vivo bioavailability in that it used too small number of patients (5 tinea pedis) and some patients were not under maximal use conditions. As diseased skin can alter the permeation characteristics and thus the in vivo bioavailability, studies conducted in subjects with healthy skin, even with scarification, can not be substituted for studies in patients with diseases. It has been the policy of the Division of Pharmaceutical Evaluation-III that if an application is otherwise acceptable from a safety and efficacy standpoint, then the assessment of *in vivo* bioavailability in patients with diseased skin can be deferred as a phase IV (post-marketing) commitment. This needs to be communicated to the sponsor.

1.2. Comments to Be Conveyed to the Sponsor

[redacted]

_____ Date: _____

Jang-Ik Lee, Pharm.D., Ph.D.
Pharmacokinetics Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

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3. SUMMARY OF CPB FINDINGS

Pharmacokinetic parameters for sertaconazole following application to the skin as 2% cream could not be determined. In Study SERT-9758, sertaconazole concentrations in plasma were below the limit of quantitation (LOQ). In Study PAZ 3018/295, intra-subject variability in the amount of sertaconazole absorbed into stratum corneum measured from skin strips were too large to determine the parameters. All pharmacokinetic studies submitted with this NDA are listed in Table I.

In animal toxicology studies, there was no evidence of toxicity at the sertaconazole dose of 39.2 mg/kg/day applied as 2% cream to the skin. Since sertaconazole concentrations were not measured in those studies, the corresponding peak concentrations in plasma at the same dose were conservatively estimated as ≥ 13 ng/mL plasma from animal pharmacokinetic studies using ^{14}C-sertaconazole nitrate cream 2%. From this indirect estimation, the no-observable-effect-level (NOEL) of sertaconazole appears to be 13 ng/mL or higher.

As conducted with a small number of patients, Study SERT-9758 demonstrated that the systemic absorption of sertaconazole through the skin from sertaconazole nitrate cream 2% is negligible. Sertaconazole concentrations in plasma following the application of the cream 0.5 g every 12 hours for a total of 13 doses per 100 cm^2 area of diseased skin in 5 patients with interdigital tinea pedis and 4 patients with tinea cruris were lower than the NOEL. Radioactivity after application of the cream 1.5 g containing 2% of ^{14}C-labelled sertaconazole nitrate to healthy or scarified skin was absent (< 20 ng/mL) in blood or plasma samples although traces of radioactivity were detected in urine and feces (Study THE/SER/91003).

Sertaconazole concentrations in the skin following the application of the cream were much higher than *in vitro* minimum inhibitory concentrations (MIC). Sertaconazole concentrations in the epidermis following the application of the cream 0.1 g to a 9 cm^2 area of the skin in the back of healthy volunteers were at the range of ng/mL, whereas the MIC against *T. rubrum* or *M. gypseum* causing tinea infections were 125 ng/mL or lower (Study PAZ 3018/295).

A high performance liquid chromatographic (HPLC) method was used in Study SERT-9758 to measure sertaconazole concentrations in plasma. The method was adequately validated and sensitive enough (limit of quantitation = 2.5 ng/mL) to detect sertaconazole concentrations at the NOEL. The HPLC method used in Study PAZ 3018/295 is marginally acceptable considering the assay matrix was cream or skin strips. The HPLC method used in Study CL-PH1a is not acceptable since the method was not satisfactorily validated (no reported inter-assay accuracy and precision) and not sensitive enough (limit of detection = 25 ng/mL) to detect the NOEL. Radioactivity assay used in Study THE/SER/91003 is not acceptable since the sensitivity equivalent to ——— , is larger than the NOEL. The simple spectroscopic method used in Study CL-PH1b without validation is not acceptable.

The to-be-marketed formulation of sertaconazole nitrate cream 2% is very similar to the clinical formulation in ingredients and manufacturing process. The sponsor added ——— ——— to the to-be-marketed formulation for ——— The sponsor provided a report that the clinical and to-be-marketed formulations were not different *in vitro* Franz cell diffusion release rates.

Table I: Pharmacokinetic Studies in NDA 21-385, Sertaconazole Nitrate Cream, 2%

Study Code	Objective	Subjects	N (M/F)	Dosage Forms	Dose and Duration	Site of Application	Remarks
SERT-9758 (US)	to determine plasma concentrations after application to diseased skin	patients with tinea pedis (5), cruris (4)	9 (9/0)	cream 2%	0.5 g / 100 cm^2 BID x 7 days	diseased skin	Only relevant study to this submission
PAZ 3018/295 (Germany)	to determine skin penetration	healthy volunteers	12 (6/6)	cream 2%	100 mg x 1	normal skin of the back	complementary to SERT-9758
THE/SER/91003 (Belgium)	to define PK (absorption, elimination) after application to skin	healthy volunteers	4 (4/0)	cream 2%	^{14}C-labeled 1.5 g x 10 days	normal and scarified skin of upper back and shoulder	unacceptable assay sensitivity
CL-PH-1 (Spain)	a) to define PK parameters after application to normal skin	healthy volunteers	8 (8/0)	cream 2%	2 - 16 g or placebo x 13 days (rising doses)	forearms	unacceptable analytical validation
	b) to determine uptake to normal skin	healthy volunteers	7 (7/0)	cream 2%	0.1 g for 24 hr x 8 zones	forearms	
[redacted]							inappropriate dosage forms, site of application -> not reviewed
[redacted]							inappropriate dosage forms, site of application -> not reviewed
[redacted]							inappropriate dosage forms, site of application -> not reviewed
[redacted]							inappropriate dosage forms, site of application -> not reviewed
[redacted]							inappropriate dosage forms, site of application -> not to be reviewed
[redacted]							inappropriate dosage forms, site of application -> not reviewed

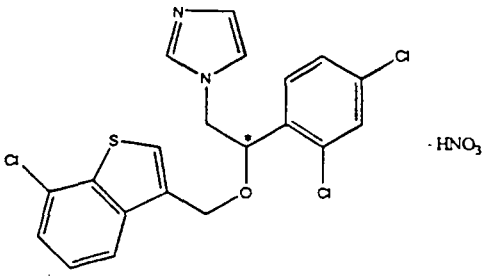
4. QUESTION-BASED REVIEW

4.1. General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Chemical Name: (±)-1-[2,4-Dichloro-β-[(7-chlorobenzo[*b*]thien-3-yl)methoxy]phenethyl]imidazole nitrate

Structure:



Molecular Weight: 500.8

Physicochemical Properties: white or almost white powder, practically insoluble in water, soluble in methanol. Imidazole residue provides antifungal activity. Benzothiophene residue provides a highly lipophillic behavior favorable for cutaneous penetration.

Formulation: 2% Cream (2 g, 15 g, 30 g)

Composition:

Table II. Ingredients in sertaconazole nitrate cream 2%

Ingredients	Function	% (w/w)
Sertaconazole Nitrate	Active	2.0
Purified Water, USP		
Methylparaben, NF		
Polyethylene Glycol Palmitostearate		
Polyoxyethylened and Glycolyzed Saturated Glycerides		
Glyceryl Isostearate		
Sorbic Acid, NF		
Light Mineral Oil, NF		
Total		**100.0**

What are the proposed therapeutic indication, dosage, route of administration and mechanism of drug action?

Indication:

Tinea pedis, the medical term for athlete's foot, is a fungal infection of the foot caused by dermatophytes, commonly referred to as ringworm. The most common species of dermatophytes are *Trichophyton*, *Epidermophyton* and *Microsporum*, which account for 90% of all skin fungal infections. These organisms grow in and remain confined to the keratinous structures of the body including the foot (tinea pedis), groin (tinea cruris), skin (tinea corporis), etc. Tinea pedis may present as variable erythema and edema, fissuring of the toe webs, scaling of the plantar surfaces, or vesicles around the toe webs and soles. Interdigital lesions may be pruritic or, when bacterial superinfection occurs, may be painful. Tinea cruris is the next most commonly involved area in dermatophyte infection, with males affected much more often than females.

Dosage and Route of Administration: twice a day for 4 weeks, topically administered to cover both affected areas and immediately surrounding healthy skin.

Mechanism of Drug Action: The activity of sertaconazole is related to the 1-(2-ary-2-substituted-ethyl)-azole residue. Although the exact mechanism of action is unknown, several mechanisms are proposed including direct cell membrane damage (fungicidal) at concentrations higher than its minimum inhibitory concentration (MIC), inhibition of cytochrome P-450-dependent ergosterol synthesis (fungistatic), and uncoupling of oxidative phosphorylation.

Antifungal Activity of Sertaconazole: The activity of sertaconazole is directed against pathogenic yeasts such as *Candida albicans*, dermatophytes (*Trichophyton, Microsporum, Epidermophyton*), opportunistic filamentous fungi (*Aspergillus*) and gram-positive organisms. The sponsor tested the *in vitro* activity of sertaconazole against 258 human pathogenic fungi and molds. The test showed that sertaconazole has a broad-spectrum antifungal activity against yeasts, dermatophytes and opportunistic fungi. The *in vitro* antifungal activity of sertaconazole was compared by its MIC to the MIC observed with ketoconazole, miconazole, fluconazole, itraconazole, amphotericin B, and clotrimazole (Table III). Mycological isolates were obtained from human tissue; dermatological fungi were obtained from human skin, hair, or nail. Sertaconazole demonstrated a superiority in MIC values to fluconazole, and inferiority to miconazole and itraconazole on fungi responsible for tinea infections (*T. rubrum*). The MIC of sertaconazole against *Candida* species is superior to that of fluconazole, inferior to that of itraconazole, and comparable to that of the other antifungal agents tested.

Table III. Comparison of *in vitro* miminimum inhibitory concentrations of sertaconazole with those of currently-marketed antifungal agents

Mycological Isolates (n)	Median MIC (µg/mL) at 24 hr						
	Sertaconazole	Ketoconazole	Miconazole	Fluconazole	Itraconazole	Amphotericin B	Clotrimazole
C. albicans (25)							
C. parapsilosis (9)							
C. lusitaniae (4)							
C. tropicalis (2)							
C. krausei (1)							
T. glabrata (8)							
M. gypseum (1)							
T. tonsurans (2)							
T. rubrum (22)	≤ 0.125	0.06	≤ 0.03	1	≤ 0.015	0.25	0.25

4.2. General Clinical Pharmacology

Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In Study SERT-9758, sertaconazole concentrations in plasma were measured using a validated high performance liquid chromatographic (HPLC) method (see 4.6. Analytical). However, the pharmacokinetic parameters of sertaconazole could not be determined because the concentrations were below the limit of quantitation (LOQ). In Study PAZ 3018/295, the amount of sertaconazole absorbed into stratum corneum was measured from skin strips using a validated HPLC method. However, pharmacokinetic parameters such as the rate of peneratration could not be determined because of large intra-subject fluctuation.

How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients? Are the study populations relevant to the proposed indication?

Study SERT-9758 conducted in a small number of patients with tinea pedis and tinea cruris contains relevant information on the extent of systemic absorption of sertaconazole from 2% cream formulation. The other 3 studies (PAZ 3018/295, THE/SER/91003, CL-PH-1) conducted in healthy volunteers (normal and scarified skin) are only complementary to Study SERT-9758 because the rate and extent of sertaconazole delivery to and penetration through healthy skin even with scarification can not be directly compared with those to and through diseased skin.

Are dosage and dosing regimen appropriate for the treatment of the proposed indication?

The data submitted in this NDA are limited to support that the dose and dosing regimen of twice a day for 4 weeks, topically administered to cover both affected areas and immediately

surrounding healthy skin are adequate. As diseased skin can alter the permeation characteristics and thus the in vivo bioavailability, studies conducted in subjects with healthy skin, even with scarification, are only complementary to studies in patients with tinea pedis. From an efficacy standpoint, Study PAZ 3018/295 conducted in healthy subjects showed that sertaconazole concentrations in the healthy epidermis were much larger than the MIC determined *in vitro* studies. The application of sertaconazole nitrate cream 2% to the skin in the back of healthy volunteers (1.1 grams per 100 cm^2 skin area) resulted in sertaconazole concentrations in the epidermis between [redacted] mg/mL from immediately to 48 hours after the application. In contrast, the average MIC values at 24 hours determined *in vitro* studies against *T. rubrum* or *M. gypseum* were 125 ng/mL or less.

From a safety standpoint, Study SERT-9758 demonstrated with a small number of patients that the extent of sertaconazole absorption through the diseased skin with tinea infection is negligible when sertaconazole cream 2% is applied in accordance with proposed dosage and administration. In this study, the cream was applied every 12 hours to the diseased skin (0.5 g per 100 cm^2 skin area). Sertaconazole concentrations in plasma obtained from serial blood samples for 72 hours after a total of 13 doses were lower than the limit of quantitation (LOQ, 2.5 ng/mL) and, therefore, the no-observable-effect-level (NOEL, 13 ng/mL) estimated in animal toxicity and pharmacokinetic studies. The number of subjects in this study is too small although the study was reinforced by adding 4 evaluable patients with tinea cruris who had much lager lesion areas (mean, 847 cm^2; range, [redacted] cm^2) to 5 patients with tinea pedis in variable lesion area (mean lesion, 93 cm^2; range, 42 - 140 cm^2).

4.3. Intrinsic Factors

The efficacy and safety of sertaconazole nitrate cream 2% have not been established in pediatric and geriatric patients. The sponsor states in the cover letter that sertaconazole nitrate cream 2% does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. The sponsor requested a full waiver of the requirement for pediatric use information. No drug-demographic interaction studies were conducted. Most pharmacokinetic studies were conducted in males.

4.4. Extrinsic Factors

Occlusive dressings can enhance the systemic absorption of sertaconazole through diseased skin. The use of occlusive dressings is discouraged.

4.5. General Biopharmaceutics

Is to-be-marked formulation equivalent to clinical formulation?

The to-be-marketed formulation of sertaconazole nitrate cream 2% is very similar to the clinical formulation in ingredients and manufacturing process. While the clinical formulation was produced at [redacted] in [redacted], the to-be-marketed formulation has been manufactured with a very similar process at DPT Laboratories in San Antonio, Texas. For the [redacted] was added to the to-be-marketed formulation.

The clinical and to-be-marketed formulations were equivalent *in vitro* Franz cell diffusion release rates (Report 54.0635.00). Table IV shows the slope ratios of the curves for the amount of sertaconazole nitrate cream diffused per unit membrane area ($\mu g/cm^2$) versus square root of sampling time (min) between the to-be-marketed (DPT Laboratories, Lot NHIN-1) and clinical batches (, Lot P-1). The release rates were similar for both lots tested as indicated by the median slopes (n = 6) for each lot: 81.28 and 78.80 $\mu g/cm^2$/square root min for NHIN-1 and Lot P-1, respectively. The 8th and 29th ordered ratios for the release rates were 0.8500 and 1.2067, respectively, and therefore, the 90% confidence interval for the median ratio was within 75 - 133.33%. Thus, the release rate of sertaconazole from the to-be-marketed batch was not statistically different from the rate from the clinical batch of sertaconazole nitrate cream 2%.

Table IV. Ratios of sertaconazole release rates ($\mu g/cm^2$/square root min) between to-be-marketed and clinical batches of sertaconazole nitrate cream 2%

		Clinical Batch (Lot P-1)					
		85.3677	**80.3392**	**67.877**	**101.9375**	**77.2465**	**70.5317**
To-Be-Marketed Batch (Lot NHIN-1)	**71.0502**	0.8323	0.8844	1.0467	0.6970	0.9198	1.0074
	65.6579	0.7691	0.8173	0.9673	0.6441	0.8500	0.9309
	77.8529	0.9120	0.9691	1.1470	0.7637	1.0079	1.1038
	84.7140	0.9923	1.0545	1.2481	0.8310	1.0967	1.2011
	93.2154	1.0919	1.1603	1.3733	0.9144	1.2067	1.3216
	100.5349	1.1777	1.2514	1.4811	0.9862	1.3015	1.4254

The study and analysis were performed based on the *in vitro* release method in the Agency's SUPAC guidance for Nonsterile Semisolid Forms. Even though the guidance is only pertinent to post approval changes, the guidance has also been applied to pre-approval changes for internal consistency at the Agency. Therefore, the application of the *in vitro* release method in the guidance appears relevant.

4.6. Analytical

What bioanalytical methods are used to assess the amount of sertaconazole in blood, urine, skin, residual cream or other study specimens?

In Study SERT-9758, a HPLC method was used with adequate validation to measure sertaconazole concentrations in plasma.

In Study PAZ 3018/295, the amount of sertaconazole in residual cream or epidermis strips was determined by a [redacted] HPLC method [redacted]

[redacted]

[redacted]. Even though some values in precision and accuracy are not [redacted] this assay method is acceptable considering technical difficulty in the [redacted]

In Study THE/SER/91003, radioactivity in study samples was measured with a [redacted]

[redacted]. This assay method is not acceptable since sertaconazole concentrations near the estimated NOEL (13 ng/mL) cannot be reliably measured.

In Study CL-PH1a, an HPLC method [redacted] was used to determine sertaconazole concentrations. [redacted]

[redacted]

Inter-assay precision and accuracy was not reported. This assay method is not acceptable because of poor validation and large intra-assay accuracy.

In Study CL-PH1b, a simple spectroscopic method that measures ultraviolet light absorbance at the wavelength of —— was used to determine sertaconazole concentrations ——

—— This is much less sensitive assay than the HPLC method used in Study CL-PH1a. Analytical validation was not reported and, therefore, this method is not acceptable.

The analytical methods used for the measurement of sertaconzole concentrations in pharmacokinetic studies submitted in this NDA are summarized in Table V.

Table V. Analytical methods used in pharmacokinetic studies for sertaconazole nitrate cream 2%

	SERT-9758	PAZ 3018/295	THE/SER/91003	CL-PH1a	CL-PH1b
Assay Method	HPLC ——	HPLC ——	Radioactivity detection	HPLC ——	UV absorbance detection
Range of Linearity	——	——	NA	——	
Regression Coeff (r^2)			NA		ND
Accuracy (%)	(deviation)				
Intra-assay	——	——	NA	——	ND
Inter-assay	——	——		ND	
Precision (CV %)					
Intra-assay	——	——	NA	——	ND
Inter-assay	——	——		ND	
Validation	Acceptable	Marginally acceptable	NA	Not acceptable	No report
Notes	LOQ < NOEL	No internal standard used	Sensitivity —— equivalent to ——	LOQ > NOEL, Assay not acceptable	

Are analytical methods sensitive enough to determine the extent of systemic absorption of sertaconazole after topical application?

In Study SERT-9758 and Study CL-PH-1a, the sponsor reported that sertaconazole concentrations in plasma after the topical application of sertaconazole nitrate cream 2% to the diseased or healthy skin were lower than the limit of quantitation (LOQ) when determined by an HPLC method. Similarly in Study THE/SER/91003 the sponsor stated that no radioactivity from plasma or blood samples was detected after the application of the cream. These do not mean that sertaconazole was not systemically absorbed or that the amount of sertaconazole absorbed, if any, was safe. Therefore, it needs to be confirmed that the analytical methods used in those studies were sensitive enough to measure the sertaconazole concentrations achieved at no-observable-effect-level (NOEL) in animal studies.

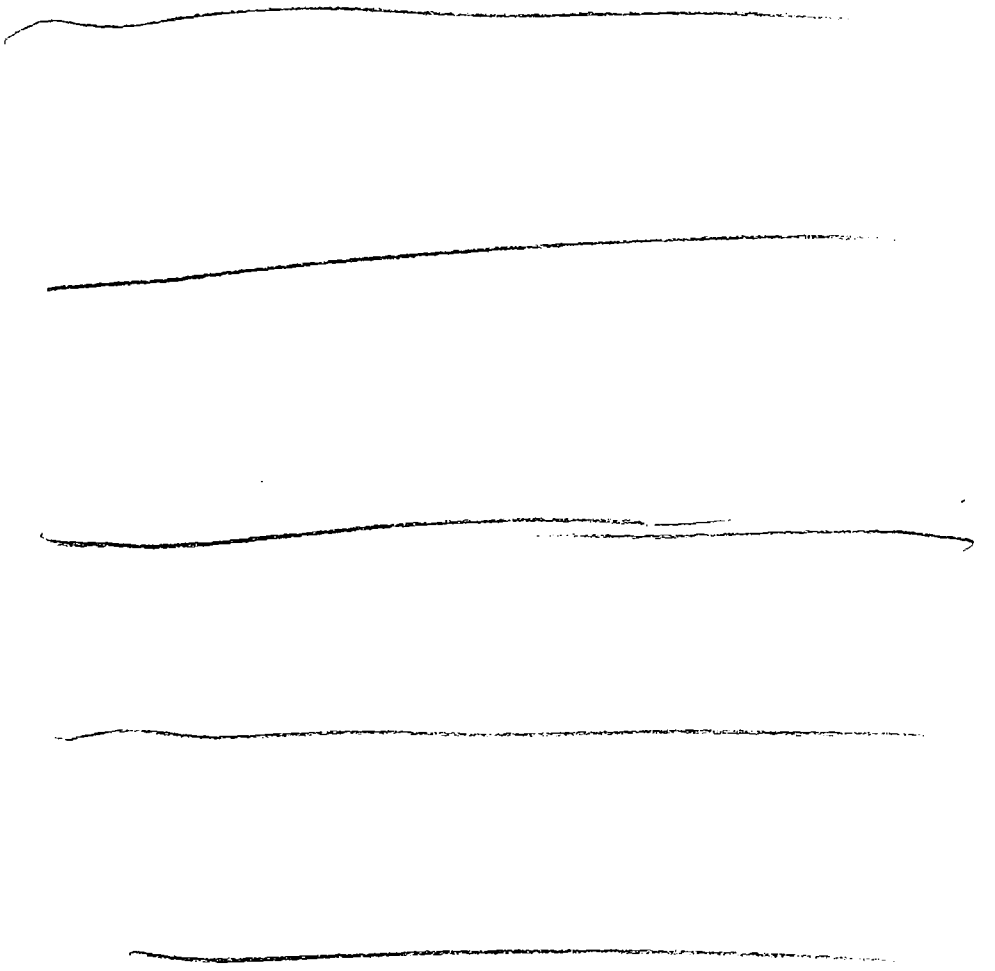
The sponsor indirectly estimated the NOEL as 8.6 ng/mL. The reviewer recalculated the NOEL using the sponsor's approach for the more accurate estimation of the NOEL. In animal toxicology studies using Sprague-Dawley rats or Beagle dogs, systemic toxicity was not evident at 39.2 mg/kg/day dose (2.0 mL/kg/day x 0.98 g/mL x 2%) of sertaconazole nitrate applied topically as 2% cream. Although the corresponding sertaconazole concentrations in plasma at the dose used in the toxicology studies were not directly measured, the concentrations can be deduced from previous animal pharmacokinetic studies in Sprague-Dawley rats using ^{14}C-sertaconazole nitrate cream 2%. The mean Cmax values obtained from the studies were 0.011% of dose per rat or 0.016% of dose per 10 mL of blood. Assuming all ^{14}C-sertaconazole molecules were intact, the Cmax can be converted to approximately 33 ng/mL. In this conversion, mean rat weight, mean plasma volume and sertaconazole dose are considered as 190 g (range in the studies, [redacted], 3.3 mL per 100 g rat weight and 10 mg per kg rat, respectively. Incidentally, the dose of 39.2 mg/kg/day used in the toxicology studies would be 3.92 times the 10 mg/kg dose used in the pharmacokinetics studies. Assuming dose-proportionality in the topical absorption of sertaconazole and ^{14}C-sertaconazole was intact, the mean Cmax value at the 39.2 mg/kg/day dose would be approximately 129 ng/mL in plasma. Although the percent contribution of intact ^{14}C-sertaconazole relative to the total peak radioactivity is not known, a conservative estimation of 10% leads to the NOEL of 13 ng/mL in plasma or larger.

Thus, the assay method used for Study SERT-9758 with LOQ of 2.5 ng/mL in plasma appears sensitive enough to measure sertaconazole concentrations around the lowest possible NOEL of 13 ng/mL in plasma estimated from animal studies. However, the assay methods used in Study THE/SER/91003 and Study CL-PH-1a with limit of detection of 20 and 25 ng/mL, respectively, are not likely to reliably detect the concentrations near the estimated NOEL.

5. DETAILED LABELING RECOMMENDATIONS

The following changes are recommended. ~~ABC~~ suggests deletion of text and ABC insertion of new text.

CLINICAL PHARMACOLOGY
Pharmacokinetics:



(To be continued in the next page)

CLINICAL PHARMACOLOGY

Pharmacokinetics: In a preliminary multiple dose pharmacokinetics study in 5 male patients with interdigital tinea pedis (range of diseased area, 42 - 140 cm^2; mean, 93 cm^2) [redacted], sertaconazole nitrate cream, 2% was topically applied every 12 hours for a total of 13 doses to the diseased skin [redacted] Sertaconazole concentrations in plasma measured by serial blood sampling for 72 hours after the thirteenth dose were below the limit of quantitation (2.5 ng/mL) of the analytical method used.

6. APPENDIX

6.1. Proposed Labeling

11 Draft Labeling Page(s) Withheld

6.2. Individual Study Reviews

Study SERT-9758

A PHARMACOKINETIC STUDY TO DETERMINE THE PLASMA CONCENTRATION OF SERTACONAZOLE FOLLOWING MULTIPLE-DOSE TOPICAL APPLICATION OF SERTACONAZOLE NITRATE 2% CREAM TO PATIENTS SUFFERING FROM TINEA PEDIS, TINEA CRURIS AND/OR TINEA CORPORIS.

Objectives:

To determine the extent of systemic absorption of sertaconazole following multiple applications as 2% cream to the diseased skin area of patients suffering from tinea pedis or tinea cruris.

Methods:

This was an open-label, one-period, multiple-dose, pharmacokinetic study. Each patient topically received a 0.5 g dose of sertaconazole nitrate cream 2% per 100 cm^2 area on pre-marked diseased skin with tinea pedis or tinea cruris. The formulation used in this study (Lot No. L-1) was identical to that used in the pivotal clinical trials (Lot No. K-4). Patients were instructed to come back every 12 hours for 7 days to receive the same dose on the same skin area (a total of 13 applications). On Days 1 and 6, a blood sample (10 ml) was collected from each patient in a heparinized tube before each morning dose. On Day 3, a blood sample was collected at 4 hours after the morning dose. On Day 7, serial blood samples were collected before dosing and at 1, 2, 4, 8, 12, 24, 48 and 72 hours after the last dose. All blood samples were processed to obtain plasma and stored at - 80 °C until analysis.

Plasma sertaconazole concentrations were determined at Mylan Pharmaceuticals Inc. in Morgantown, WV using a high performance liquid chromatographic (HPLC) method —— The assay was linear at the concentration range of —— . The inter-day precision (coefficient of variation, %) of the assay was —— The inter-day accuracy (deviation, %) varied within —— of the nominal concentration of sertaconazole. A detailed review on analytical method is in 4.6. Analytical.

Inclusion/Exclusion Criteria: Adult male and non-pregnant non-lactating female patients who were clinically diagnosed with interdigital tinea pedis, tinea cruris and/or tinea corporis were recruited in this study. Patients were excluded when they had been treated with any topical antifungal agents within 14 days, any investigational drugs other than antifungal drugs within 30 days, or systemic antifungal agents within 3 months prior to the initial dose of sertaconazole nitrate cream. These and other inclusion and exclusion criteria are relevant to this study.

Results:

The study was conducted at —— in 1998. Ten male patients aged between 19 and 37 years old were enrolled and completed the study. Five patients were clinically diagnosed as interdigitan tinea pedis and five as tinea cruris. The total lesion areas were at the ranges of 42 - 140 cm^2 (mean, 93 cm^2) and —— (mean, 847 cm^2) in patients with

interdigitan tinea pedis and tinea cruris, respectively. Fungal cultures showed that all patients enrolled were infected with *Trichophyton rubrum* except one (tinea cruris) with negative culture result and excluded from data analysis. All patients enrolled had positive KOH wet mount preparation. Each sertaconazole dose ranged between 0.21 and 4.73 g for a total of 13 applications.

Under the analytical capacity of this study, sertaconazole concentrations in plasma were not measurable following twice daily applications of sertaconazole nitrate cream 2% for two weeks onto the diseased skin with interdigital tinea pedis as well as tinea cruris except a pre-dose concentration (2.9 ng/mL) on Day 6 for Subject No. 002. One adverse event was reported during the study: a moderate headache.

Conclusion:

- Sertaconazole concentrations in plasma were lower than the limit of quantitation (2.5 ng/mL) following the topical application of sertaconazole cream 2% every 12 hours for a total of 13 doses to the diseased skin (0.5 g per 100 cm^2 area) in 5 male patients with interdigital tinea pedis (mean lesion area, 93 cm^2) or 4 male patiets with tinea cruris (mean lesion area, 847 cm^2).

Reviewer's Comment:

- The number of study subjects is too small to draw firm conclusion although the study was reinforced by adding 4 evaluable patients with tinea cruris that involves much lager lesion area to 5 patients with tinea pedis, the proposed indication. Only male patients were studied.
- The range of diseased area in tinea pedis was wide (42 - 140 cm^2). The study patients with diseased area near 42 cm^2 do not appear to be under maximal use conditions.
- Sertaconazole concentrations in plasma lower than the limit of quantitation (2.5 ng/mL) does not mean safe but unquantifiable. Upon the Agency's request, the sponsor provided the information that the analytical method was sensitive enough to measure sertaconazole concentrations achieved at the no-observable-effect-level (NOEL $\geq$ 13 ng/mL) estimated from animal studies (see 4.6. Analytical).
- It is not known why a pre-dose concentration of sertaconazole on Day 6 in one subject was higher than the limit of quantitation. However, this is not likely to affect the overall conclusion since the concentration was still lower than the NOEL.

Study PAZ 3018/295

PERCUTANEOUS ABSORPTION OF SERTACONAZOLE FOLLOWING SINGLE TOPICAL ADMINISTRATION OF 2 MG CREAM TO THE SKIN OF THE BACK IN 6 MALE AND 6 FEMALE HEALTHY SUBJECTS

Objectives:

To determine the rate and extent of sertaconazole penetration from 2% cream into and through the stratum corneum/lucidum at the skin of the back in normal healthy volunteers

Methods:

This was one period single administration study with variable time intervals of the topical application of sertaconazole nitrate cream 2% to enable intraindividual comparisons for percutaneous absorption of sertaconazole. Ten different areas of 3 x 3 cm^2 on the back of the subjects (5 each side of the spine) were treated with 100 mg of 2% cream (2 mg as sertaconazole nitrate, 9 areas) or placebo (1 area). To determine the rate of penetration, residual cream was removed one by one from the 9 areas with Latin squares randomization at 0 (instant removal), 0.5, 1, 3, 6, 12, 24, 32 and 48 hours after application. Immediately after removal of residual cream, the stratum corneum/lucidum was stripped from respective application area with adhesive tape (3 x 3 cm^2) until the skin were evenly covered with exudates (9 - 18 strips). The strips were divided into 3 equal fractions of upper, middle and lower layers from outside to inside.

The amount of sertaconazole in residual cream and epidermis strips was determined by a high performance liquid chromatographic (HPLC) method [redacted]
The lower limit of quantitation was [redacted] per strip fraction. The assay was linear ([redacted] at a range of [redacted] for strip fractions and residual cream, respectively. Within-day precision (coefficient of variation, %) and accuracy (%) calculated from standard curves were [redacted] respectively. Between-day precision and accuracy were [redacted], respectively. Analytical error was estimated by subtracting the amount of sertaconazole recovered from skin surface and skin strips at time 0 from the amount of sertaconazole that was initially applied to the skin.

The apparent mean rate of penetration was estimated assuming first order kinetics. The apparent average drug level in the stratum corneum/lucidum was estimated converting amount per 3 x 3 cm^2 x 18 µm to amount per mL. The total amount of sertaconazole penetrated into skin was calculated by subtracting the amount recovered from residual cream from the amount initially applied to the skin and correcting for the analytical error. The amount of sertaconazole passed stratum corneum and penetrated into the deep layers of skin was estimated by subtracting the amount recovered from skin strips from the total amount penetrated into the skin. All amounts were expressed as % of dose applied.

Inclusion/Exclusion Criteria: Healthy Caucasian volunteers aged between 18 and 45 years old were included. Pregnant or lactating females, drug or alcohol abusers, and subjects who have any skin disease or took any medication within 14 days prior to this study, were excluded. Other inclusion and exclusion criteria were appropriate to this study.

Results:

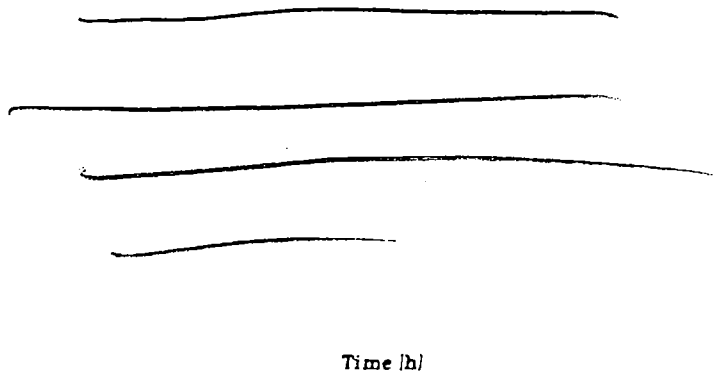
This study was performed by [redacted], in 1995. A total of 12 healthy Caucasian volunteers (6 males, 6 females) aged between 21 and 40 years old was enrolled.

Sertaconazole nitrate 1.87 ± 0.14 mg (88.9 ± 2.3 % of dose) was recovered from residual cream following instant removal after the application of sertaconazole nitrate 2.10 ± 0.15 mg as 2% cream on the normal skin in the back (Table 2-1). The amount of sertaconazole nitrate recovered from the residual cream decreased as the duration of application went longer: 82.5 ± 4.5 %, 77.7 ± 8.6 %, 55.7 ± 16.3 % and 52.5 ± 8.5 % of dose after 0.5, 6, 24 and 48 hours, respectively (Table 2-1). The relationship between the amount of sertaconazole recovered and the duration of application demonstrated a steady decrease with exponential trend (Figure 2-1). However, the rate of penetration could not be determined due to a large intra-subject fluctuation of the amount recovered over time. The apparent half-life of the recovery estimated from its mean curve was approximately 60 hr.

Table 2-1. Mean recovery of sertaconazole (% dose) from skin surface and stratum corneum/lucidum, and amount penetrated into skin following the application of sertaconazole nitrate cream 2% (N=12)

T	Mean Recovery FROM SKIN SURFACE	Mean Amount in Stratum corneum/lucidum	Mean Portion not recovered by Assay	Total Mean Amount penetrated in Human Skin	Mean Amount penetrated in Human Skin except for Stratum corneum
	exact	exact	exact	estimated	estimated
[h]	[% of dose]				
0.0*	88.9	1.1	10.0	1.1	0.0
0.5	82.5	5.3	12.2	7.5	2.2
1.0	82.5	5.2	12.3	7.5	2.3
3.0	76.5	6.9	16.6	13.5	6.6
6.0	77.7	6.5	15.8	12.3	5.8
12.0	65.9	6.3	27.8	24.1	17.8
24.0	55.7	10.7	33.5	34.2	23.5
32.0	52.6	7.2	40.1	37.4	30.1
48.0	52.4	6.9	40.7	37.6	30.7

Figure 2-1. Spaghetti plot for the recovery of sertaconazole nitrate from residual cream over time of application.



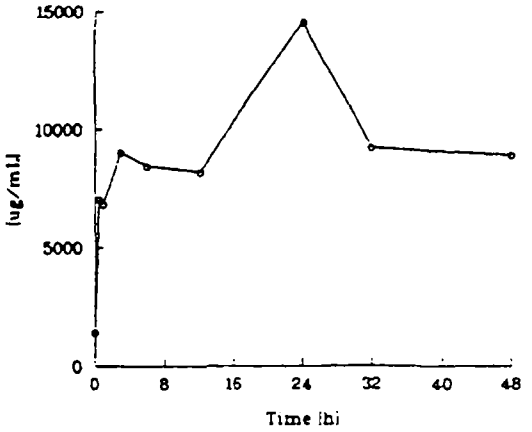
Shortly after application of the cream, sertaconazole was detected in the upper (21.0 ± 22.6 µg, 1.0 ± 1.0 % of dose) and middle fraction of skin strips (1.8 ± 6.4 µg, 0.1 ± 0.3 % of dose) (Table 2-2). At 0.5 hour post application, 103 ± 63.7 µg (4.7 ± 2.9 %), 9.2 ± 13.8 µg (0.4 ± 0.6 %) and 2.2 ± 7.5 µg (0.1 ± 0.4 % of dose) of sertaconazole were stripped in the upper, middle and lower fractions, respectively. Sertaconazole recovery appears to reach a plateau around 0.5, 3, and 3 hours after application at the upper, middle and lower fraction of strip, respectively (Table 2-2). A gradient from site of application to the epidermis was present at the plateau decreasing from the upper (approx. 100 - 120 µg, 5.0 - 6.0 % of dose) to middle (approx. 20 - 35 µg, 1.0 - 1.8 %) and to lower fraction of strips (approx. 5 - 15 µg, 0.3 - 0.8 %). There was an extremely high or low recovery of sertaconazole in a few time points (3, 12 and 24 hr post exposure in lower, middle and upper fractions, respectively).

Table 2-2. Recovery of sertaconazole from upper, middle and lower fractions of skin strips from stratum corneum/lucidum following the application of sertaconazole nitrate cream 2% (N=12)

T [h]	RECOVERY IN STRATUM CORNEUM STRIPS [% of Dose] UPPER		[% of Dose] MIDDLE		[% of Dose] LOWER	
	MEAN	SD	MEAN	SD	MEAN	SD
0.00 Placebo	0.0	0.0	0.0	0.0	0.0	0.0
0.00	1.0	1.0	0.1	0.3	0.0	0.0
0.50	4.7	2.9	0.4	0.6	0.1	0.4
1.00	4.3	1.9	0.6	0.8	0.2	0.6
3.00	5.0	2.1	1.2	0.9	0.7	0.8
6.00	4.9	2.4	1.3	0.7	0.4	0.6
12.00	4.9	1.6	1.1	0.7	0.2	0.6
24.00	8.6	9.1	1.6	1.0	0.5	0.7
32.00	5.7	2.7	0.9	1.3	0.6	1.0
48.00	5.4	2.7	1.1	1.0	0.4	0.8

The apparent average sertaconazole concentration in stratum corneum/lucidum was estimated as 1.4 and 7.0 mg/mL immediately and at 0.5 hr after application of sertaconazole nitrate cream 2% (100 mg). A plateau was reached after 3 hr with approx. 9.0 mg/mL except for an extraordinanarily high concentration measured at 24 hr after application (Figure 2-2). The concentrations in the stratum corneum were much larger than the MIC values determined *in vitro* studies (see Antifungal Activity in QBR).

Figure 2-2. Mean concentrations of sertaconazole in stratum corneum estimated from the amount recovered from skin strip.



At time 0, 90.0 ± 2.2 % of sertaconazole dose was recovered analytically (Table 2-1) and, therefore, the analytical error was assumed to be 10%. Under this assumption, the mean relative portion of sertaconazole nitrate that penetrated stratum corneum/lucidum and deep layers of skin increased from 1.1% at time 0 to 24.1%, 34.2% and 37.6% of dose at 12, 24 and 48 hours after the application of 2% cream, respectively (Table 2-1). The mean portion that penetrated into deep layers of skin was assumed to be 0 % at time 0, and increased to 17.8%, 23.5% and 30.7% of dose after 12, 24 and 48 hours, respectively (Table 2-1). No adverse events were reported.

Conclusions:

- The application of approximately 0.1 g of sertaconazole nitrate cream 2% (2 mg as sertaconazole nitrate) to the skin area of 9 cm^2 in the back of healthy volunteers led to the penetration of approximately 38% of dose over 48 hours.
- Approximately 6 - 7% of dose (0.12 - 0.14 mg) stayed in stratum corneum with saturation between 3 and 48 hours after application of the cream.
- Sertaconazole concentrations in the epidermis maintained at a range of ———— which is much larger than *in vitro* MIC values (125 ng/mL or less), from immediately to 48 hours after application.
- Approximately 31% of sertaconazole dose penetrated into deep layers of skin.

Reviewer's Comments:

- This study provides useful information on the extent of sertaconazole absorption from 2% cream to and through the healthy skin. However, these results are only complementary to Study SERT-9758 since the extent of sertaconazole absorption to and through healthy skin is not necessarily the same as that to and through diseased skin (tinea pedis).

Study THE/SER/91003

INVESTIGATION OF THE PHARMACOKINETIC PROFILE OF ^{14}C-SERTACONAZOLE FOLLOWING A SINGLE TOPICAL APPLICATION IN NORMAL AND SCARIFIED SKIN OF HEALTHY VOLUNTEERS

Objectives:

To investigate the extent of absorption and routes of elimination of sertaconazole following a single and/or repeated topical application to the scarified and normal skin of healthy volunteers.

Methods:

This was a mass balance study with topical application of ^{14}C-labelled sertaconzole. Each study subject received approximately 1.5 g of cream containing 2% of ^{14}C-sertaconazole nitrate (Batch No. 2792-128, final specific activity = 3.28 mCi/mmol) twice as a single topical application to the normal and scarified skin. Skin area applied was 250 cm^2 of upper back and shoulder region. The mean dose of ^{14}C-sertaconazole nitrate was 23.0 ± 1.01 mg (58.8 ± 2.75 µCi) and 23.9 ± 0.6 mg (60.1 ± 1.6 µCi) in the normal and scarified skin, respectively. The two applications were separated by at least one month. Scarification was done on the same 250 cm^2 area of the normal skin using a sterile needle drawing 5 horizontal and 12 vertical lines with a distance of 2 cm on the delimited surface.

Blood samples (approximately 30 ml) were collected at pre-dose, and 1, 3, 6 and 12 hours, and 1, 1.5, 2, 3, 4, 6 and 10 days after application of the cream. An aliquot (1 mL) of blood was stored at 4°C for immediate analysis. Remaining samples were centrifuged and resultant plasma stored at - 20 °C until analysis. All urine was collected following the application after the bladder was emptied, pooled as 24-hour samples for 7 days, and stored at - 18 °C until analysis. All feces were collected for a period of 7 days following the application. Fecal samples were returned daily and extracted using ethanol. The extracts were analyzed or stored frozen until further analysis. Radioactivity that still present on application site was measured on Days 6 and 10 by a tape stripping technique. Gauze dressings, gloves and all other materials used for application or removal of cream were collected for radioactivity measurement.

Radioactivity in study samples was measured with a [redacted] mean values were used for calculations. When the difference between the two measurements was too high, supplementary aliquots were measured. Each biological sample was pre-processed with each relevant technique before radioactivity measurement. Radioactivity for blank samples were also measured in parallel and subtracted from that for corresponding study samples. The radioactivity present in each sample was measured after the addition of [redacted] The sensitivity of the assay was [redacted] and equivalent to [redacted] plasma or blood.

Inclusin/Exclusion Criteria: Healthy Caucasian male volunteers aged between 20 and 30 years old were included. Alcohol or drug addicts and heavy smokers (more than 10 cigarettes per day) were excluded. Subjects who had any pronounced hair growth or physical damage / abnormality at the intended sites of skin, applied any topical drugs to the intended sites during the preceding 4

weeks, or participated in the evaluation of any drug in preceding 3 months were not allowed to enroll the study. Other inclusion/exclusion criteria were relevant to the study.

Results:

The study was conducted at [redacted] in 1991. A total of 4 healthy male volunteers aged between 26 and 30 years old completed the study.

The total radioactivity recovered in the material used for application and removal of the cream corresponded to 89.9% (range, [redacted]) of the administered dose in normal skin and 89.1% (range, [redacted]) in scarified skin. No radioactivity was detected in blood and plasma samples. Some traces of radioactivity were detected in the urine and feces samples of the following two subjects:

- Subject No. 40' [redacted] of administered dose in the urine samples collected between 1 and 2 days after the first application (normal skin)
- Subject No. 5 [redacted], of administered dose in the urine samples collected during the first 24 hours and [redacted] in feces collected between 2 and 3 days after the second application (scarified skin)

Sertaconazole may be metabolized to non-extractable metabolites since no radioactivity was observed in the extracted fraction of urine samples. The presence of traces of radioactivity in the stripping samples may indicate that some drug could stay in the upper levels of the skin (stratum corneum). No adverse effect was recorded.

Conclusions:

- Radioactivity following the application of approximately 1.5 g of the cream containing 2% of ^{14}C-sertaconazole nitrate to the healthy or scarified skin was absent in blood and plasma samples. In contrast, traces of radioactivity were detected in urine and feces.
- It is estimated that less than 0.5% of dose administered as 2% cream was absorbed even on scarified skin.

Reviewer's Comments:

- The systemic absorption of sertaconazole through normal or scarified skin is not necessarily the same as that through diseased skin (tinea pedis).
- The assay method used in this study is not acceptable (see 4.6. Analytical). The method with a sensitivity of [redacted] (equivalent to [redacted] plasma) cannot reliably measure sertaconazole concentrations near the no-observable-effect-level (NOEL) estimated from animal studies that can be as low as 13 ng/mL.

Study CL-PH-1a & CL-PH-1b

PHARMACOKINETICS AND SAFETY OF SERTACONAZOLE APPLIED AS REPEATED AND INCREASING TOPICAL DOSES FOR 14 DAYS.

Objectives:

To determine the systemic absorption and skin uptake of sertaconazole after topical application to the skin.

Methods:

This study consists of two parts: systemic absorption study (CL-PH-1a) and skin uptake study (CL-PH-1b). Sertaconazole nitrate cream 2% was administered topically to the skin at increasing doses for 14 days. The skin uptake and systemic absorption of sertaconazole were determined on the first and last day of the study, respectively.

- Day 1 (sertaconazole skin uptake): Sertaconazole 0.08 g (4 g as 2% cream) as a single dose was distributed over 8 zones of 3 x 3 cm on the anterior surface of both forearms. The cream was deposited in the zone and applied for one minute by massage with a plastic thimble to obtain maximum penetration. The actual amount applied was calculated from the amount applied to each zone minus the residue adhering to the plastic thimble. In order to determine the bioavailability of sertaconazole, residual cream was collected from each zone by washing with ethanol-impregnated gauze at different times (0, 1, 2, 4, 6, 8, 12 and 24 hours). One zone was washed at each time. The gauze was collected in glass containers and sealed with paraffin until analyzed. Sertaconazole uptake was determined as the difference between the actual amount of sertaconazole initially applied and the amount recovered from ethanol washings.

- Days 2-4: Sertaconazole 0.04 g as a single daily dose on the anterior surface of one forearm.

- Days 5-7: Sertaconazole 0.08 g as a single daily dose on the anterior surface of one forearm.

- Days 8-10: Sertaconazole 0.16 g per day divided into two applications at an interval of 12 hours to the anterior surface of both forearms (0.04 g each).

- Days 11-13: Sertaconazole 0.24 g per day divided into two applications at an interval of 12 hours to the anterior surface of both forearms (0.06 g each).

- Day 14 (sertaconazole systemic absorption): Sertaconazole 0.32 g as a single application (0.08 g on one forearm and arm, and 0.24 g on the surface of the back). Venous blood samples were obtained at 0, 1, 2, 4, 6, 8, 12, 24 hours after application of the drug to study the basic pharmacokinetic parameters. Urine was also collected for 24 hours, divided into the following periods: 0-4 hours and 12-24 hours. The cream was applied by the volunteer himself, massaging until the residues disappeared from the skin. The investigators applied it to the back and shoulders.

Inclusin/Exclusion Criteria: Translation is not available.

Results:

This study was conducted at the [redacted] in 1987. Eight healthy male volunteers aged 18-29 years (mean, 24 years) were completed this study. The Batch No. z-01 of sertaconazole nitrate cream 2% was used. No adverse events were reported.

Sertaconazole Systemic Absorption (CL-PH-1a): Sertaconazole concentrations in plasma and urine were determined using a high performance liquid chromatographic (HPLC) method [redacted]. A calibration curve was constructed at a range of sertaconazole nitrate concentrations of [redacted] ng/mL. The minimum concentration of sertaconazole that can be reliably detected relative to blank was [redacted] plasma or urine. Samples from all subjects were analyzable. No plasma or urine samples analyzed showed significantly different response from the blank. The assay method was not adequately validated (see 4.6. Analytical).

Sertaconazole Skin Uptake (CL-PH-1b): Sertaconazole concentrations in methanol solution were determined using a ultraviolet/visible spectroscopic method. A calibration curve was drawn at a range of sertaconazole nitrate concentrations of [redacted]. Samples from seven subjects were analyzable. The penetration capacity of sertaconazole for 24 hours after the first dose ranged from [redacted] of the dose. Analytical validation was not reported. (see 4.6. Analytical).

Conclusion:

- Sertaconazole concentrations in plasma at any serial sampling points 14 days after multiple escalating doses of sertaconazole nitrate cream 2% were lower than limit of detection (25 ng/ml).
- The amount of sertaconazole recovered from urine was estimated as ≤ 0.01 - 0.02 % of dose.
- The penetration capacity of sertaconazole to the normal skin for 24 hours after the first topical application of sertaconazole cream 2% ranged form 82% to 89% of the dose.

Reviewer's Comment:

- The assay methods used in this study are not acceptable in terms of sensitivity and validation (see 4.6. Analytical). The method with limit of detection of 25 ng/mL or larger does not reliably measure sertaconazole concentrations near the no-observable-effect-level (NOEL) estimated from animal studies that can be as low as 13 ng/mL.
- The extent of systemic absorption and skin uptake of sertaconazole determined in this study after application to the normal skin can not be extrapolated to those expected after application to the diseased skin (tinea pedis).
- Overall, this study is not adequate to predict the extent of systemic absorption or skin uptake of sertaconazole from 2% cream through the diseased skin with interdigital tinea pedis (proposed indication).

Report 54.0635.00

A COMPARISON OF THE *IN-VITRO* FRANZ CELL DIFFUSION RELEASE RATES OF SERTACONAZOLE CREAM

Objectives:

To compare the *in-vitro* diffusion rates of sertaconazole between the clinical and to-be-marketed batches of sertaconazole nitrate cream 2%

Methods:

The *in-vitro* diffusion release rates for sertaconazole were determined on a to-be-marketed batch of sertaconazole nitrate cream 2% manufactured at DPT Laboratories (Lot NHIN-1, test) and a clinical batch manufactured at [redacted] (Lot P-1, reference). The two batches were compared for the rates according to the *in vitro* release test method in the Agency's SUPAC guidance for Nonsterile Semisolid Dosage Forms.

A vertical Franz cell system was used in this study. [redacted]

The receptor fluid samples were analyzed for sertaconazole nitrate content by a [redacted] high performance liquid chromatographic (HPLC) method [redacted] validate the linearity. The coefficient of variation (CV) for a set of response/concentration values were [redacted] and the correlation coefficients was greater than [redacted] The precision of the Franz cell system was [redacted] (CV) using [redacted] working standard of sertaconazole nitrate.

The amount of sertaconazole nitrate diffused per cm^2 membrane area was plotted versus the square root of the respective sampling times. Linear regression analyses of these data to obtain slopes were performed on both lots. The 36 individual test/reference slope ratios were calculated.

Results:

Table 5-1 shows the slope ratios of the curves for the amount of sertaconazole nitrate cream diffused per unit membrane area ($\mu g/cm^2$) versus square root of sampling time (min) between the to-be-marketed and clinical batches. The release rates were similar for both lots tested as indicated by the median slopes (n = 6) for each lot: 81.28 and 78.80 $\mu g/cm^2$/square root min for NHIN-1 and Lot P-1, respectively. The 8^{th} and 29^{th} ordered ratios for the release rates were

0.8500 and 1.2067, respectively, and therefore, the 90% confidence interval for the median ratio was within 75 - 133.33%.

Table 5-1. Ratios of sertaconazole release rates (μg/cm²/square root min) between to-be-marketed and clinical batches of sertaconazole nitrate cream 2%

		Clinical Batch (Lot P-1)					
		85.3677	80.3392	67.877	101.9375	77.2465	70.5317
To-Be-Marketed Batch (Lot NHIN-1)	71.0502	0.8323	0.8844	1.0467	0.6970	0.9198	1.0074
	65.6579	0.7691	0.8173	0.9673	0.6441	0.8500	0.9309
	77.8529	0.9120	0.9691	1.1470	0.7637	1.0079	1.1038
	84.7140	0.9923	1.0545	1.2481	0.8310	1.0967	1.2011
	93.2154	1.0919	1.1603	1.3733	0.9144	1.2067	1.3216
	100.5349	1.1777	1.2514	1.4811	0.9862	1.3015	1.4254

Conclusion:

- The release rate for sertaconazole from a to-be-marketed batch (DPT Laboratories, Lot NHIN-1) of sertaconazole nitrate cream 2% was not statistically different from the rate from a clinical batch.

Reviewer's Comment:

- The differences between the to-be-marketed (Lot NHIN-1) and clinical batches (Lot P-1) are their manufacturing sites and an inactive ingredient. Whereas Lot P-1 was manufactured at [redacted] Lot NHIN-1was produced at DPT Laboratories, San Antonio, Texas under the essentially same manufacturing process. Lot NHIN-1 contains [redacted]
- Even though the SUPAC guidance is only pertinent to post approval changes, the guidance have also been applied for pre-approval changes for internal consistency at the Agency. Therefore, the application of *in vitro* release test method in the guidance appears relevant.
- No difference in drug release rate shown in this *in vitro* study supports that the change in manufacturing site and the addition of [redacted] are not likely to affect the safety and efficacy profile of sertaconazole nitrate cream 2%. Based on the SUPAC guidance and CFR 21 §320.22, bioequivalence studies can be waived for this pre-approval change.

6.3. OCPB Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-385	Brand Name	to be determined
OCPB Division (I, II, III)	III	Generic Name	sertaconazole nitrate cream, 2%
Medical Division	HFD-540	Drug Class	antifungal
OCPB Reviewer	Jang-Ik Lee	Indication(s)	[redacted]
OCPB Team Leader	E. Dennis Bashaw	Dosage Form	cream 2% (2 g,15 g, 30 g)
		Dosing Regimen	BID x 4 wks
Date of Submission	09/28/01	Route of Administration	topical
Estimated Due Date of OCPB Review	03/31/02	Sponsor	Mylan Pharmaceuticals Inc.
PDUFA Due Date	07/28/02	Priority Classification	1S
Division Due Date	04/30/02		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:	X	3	1	See other comments
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3	1	See other comments
multiple dose:	X	2	1	See other comments
Patients-				
single dose:	X	3		See other comments
multiple dose:	X	1	1	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics	X	1		See other comments
Pediatric development plan				
Literature References				
Total Number of Studies		10	4	

Filability and QBR comments		
	"X" if yes	Comments
Application fileable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included) FDA letter date if applicable.
QBR questions (key issues to be considered)	1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? 2. What are the proposed therapeutic indication, dosage, route of administration and mechanism of drug action? 3. Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? 4. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients? Are the study populations relevant to the proposed indication? 5. Are dosage and dosing regimen appropriate for the treatment of the proposed indication? 6. Is to-be-marked formulation equivalent to clinical formulation? 7. What bioanalytical methods are used to assess the amount of sertaconazole in blood, urine, skin, residual cream or other study specimens? 8. Are analytical methods sensitive enough to determine the extent of systemic absorption of sertaconazole after topical application?	
Other comments or information not included above	Some studies are not relevant to the indication being pursued in this submission and, therefore, were not included in this review.	
Primary reviewer Signature and Date	Jang-Ik Lee (5/3/02)	
Secondary reviewer Signature and Date		

CC: NDA 21-385, HFD-850 (P. Lee), HFD-540 (CSO), HFD-880 (TL, DD, DDD), CDR

End of Document

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

/s/

Jang-Ik Lee
5/3/02 11:23:21 AM
BIOPHARMACEUTICS
Added a section of in vitro drug release test
after briefing
added words in recommendation and labeling

Dennis Bashaw
5/3/02 07:30:12 PM
BIOPHARMACEUTICS

Addendum to Review

May 30, 2002

To: Jon Wilkin, M.D., Director, HFD-540

From: Ike Lee, Pharm.D, Ph.D., HFD-880

Through: E. Dennis Bashaw, Pharm.D., PK Team Leader

RE: Sertaconazole PK review

In the pk review written by Dr. Ike Lee the following comment is provided on page 39 of the review:

> "No difference in drug release rate shown in this in vitro study supports that the change in manufacturing site and the addition of [redacted] are not likely to affect the safety and efficacy profile of sertaconazole nitrate cream 2%. Based on the SUPAC guidance and CFR 320.22, bioequivalence studies can be waived for this pre-approval change."

After consultation with the Dermatological Division medical staff, it was decided that this comment needs clarification. It was the intent of this comment to indicate that the in vitro testing was sufficient to indicate that there would not be major change in the release rate of active drug from the proposed cream due to either the change in manufacturing site or the addition o' [redacted] The portion of the comment related to safety was meant to imply that as there was no change in the in vitro release of sertaconazole there should be no change in the safety of the drug product attributable to the active ingredient. It is possible, however, that the presence of [redacted] self might have a deleterious impact on the safety of the drug product due to [redacted] It is also possible that in [redacted] In either event, the current in vitro methods used to assess drug release are incapable of making such a determination either way.

In light of this, the addition of [redacted] o the final drug product does carry with it (itself) a potential [redacted] that can only be assessed through a head-to-head clinical safety trial of [redacted] ontaining drug product vs. [redacted] drug product. Such a study could be conducted as a phase IV commitment. As to the design and timeline for implementation of such a study we defer to the Dermatological Division medical staff for their guidance in this area.

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/s/

Jang-Ik Lee
5/30/02 04:57:38 PM
BIOPHARMACEUTICS
Addendum regarding [redacted]
Adenum to Review

Dennis Bashaw
5/30/02 05:02:10 PM
BIOPHARMACEUTICS