

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203567Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Division of Anti-Infective and Ophthalmology Products
Clinical Microbiology Consultation, Labeling Review

NDA 203567

Date Review Completed: 17 May 2014

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Date Original NDA Received by CDER: 26 July 2012

Date Assigned: 17 August 2012

Date Review Completed: 17 May 2014

Reviewer: Kerry Snow MS, MT(ASCP)

APPLICANT

Dow Pharmaceutical Sciences, Inc.
1330 Redwood Way
Petaluma, CA 94954-7121
Barry M. Calvarese, MS
Vice President
Regulatory and Clinical Affairs

DRUG PRODUCT NAME

Proprietary name: JUBLIA™

Established name: Efinaconazole Solution, 10%

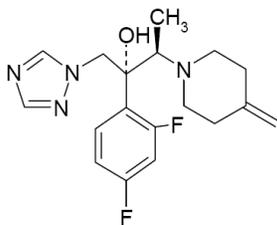
Non-proprietary name: IDP-108 Topical Solution or KP-103 Topical Solution

Chemical name: C₁₈H₂₂F₂N₄O

Molecular formula: (2R,3R, 3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol

Molecular weight: 348.39

Chemical structure:



PROPOSED INDICATION

Treatment of mild to moderate onychomycosis of the toenails

PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION

Form: liquid

Strength: 10%

Route of Administration: topical

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DISPENSED

Rx

RELATED DOCUMENTS

none

REMARKS

The Applicant filed a New Drug Application for Efinaconazole Solution 10% for the once daily treatment of onychomycosis (tinea unguium) on 26 July 2012. The Division of Dermatology and Dental Products consulted the Division of Anti-Infective Products to review clinical microbiological information and conclusions, included in that submission. The consultation was completed and filed on 4 March 2013. The Application was deemed approvable, from a clinical microbiology perspective, provided that the Applicant address proposed changes to the product labeling (see Clinical Microbiology review dated 4 March 2013).

The Applicant re-submitted NDA 203567 on 20 December 2013 to address deficiencies noted in the CMC review of the original Application. No new clinical microbiology information was included in that resubmission.

CONCLUSIONS

From a clinical microbiology perspective, the Application is approvable, provided that changes are made to the proposed product labeling, as described below.

PROPOSED LABEL

The Agency recommends the following changes to the proposed labeling:

1. Change (b) (4) to “an azole antifungal” (preference stated by DDDP).
2. Strike discussion of (b) (4) from the Mechanism of Action section. Studies performed to evaluate the (b) (4) were inconclusive (b) (4) and no clinical relevance of this finding has been established.
3. Strike discussion of (b) (4) from the Mechanism of Action section. The terms are very broad and may be misleading. (b) (4) Finally, the clinical relevance of such descriptions is unclear.
4. Change “(b) (4)%” to “≥90%” in the Activity In Vitro and In Vivo section.

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5. Delete [redacted] (b) (4)
6. Delete [redacted] (b) (4) section. This information is non-informative for the purposes of product labeling.
7. Strike [redacted] (b) (4) from the Resistance section. This statement is speculative, not well supported by data included in the NDA submission, and may be misleading, clinically.
8. Delete [redacted] (b) (4) section. The section is non-informative.

The changes to the proposed labeling (Section 12.4) are presented below (bold font indicates additions, double-strikethrough font indicates deletions).

12.4 Microbiology

Mechanism of Action

Efinaconazole is [redacted] (b) (4). Efinaconazole inhibits fungal lanosterol 14 α -demethylase involved in [redacted] (b) (4)

Activity In Vitro and In Vivo

Efinaconazole has been shown to be active against isolates of the following microorganisms, both *in vitro* and in clinical infections. Efinaconazole exhibits *in vitro* minimum inhibitory concentrations (MICs) of 0.06 μ g/mL or less against most [redacted] (b) (4) ($\geq 90\%$) of isolates of the following microorganisms:

Trichophyton mentagrophytes

Trichophyton rubrum

[redacted] (b) (4)

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(b) (4)

(b) (4)

(b) (4)

Efinaconazole drug resistance development was studied *in vitro* against *T. mentagrophytes*, *T. rubrum* and *C. albicans*. Serial passage of fungal cultures in the presence of sub-growth inhibitory concentrations of efinaconazole increased the MIC by up to 4-fold; (b) (4). The clinical significance of these *in vitro* results is unknown.

(b) (4)

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(b) (4)

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/s/

KERRY SNOW
05/17/2014

MEMORANDUM



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

DATE: 10 January 2014

TO: NDA 203567

FROM: Bryan S. Riley, Ph.D.
Team Leader (Acting)
OPS/New Drug Microbiology Staff

THROUGH: Stephen E. Langille, Ph.D.
Master Review Microbiologist
OPS/New Drug Microbiology Staff

cc: Strother D. Dixon
Regulatory Project Manager
OND/DDDP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Efinaconazole Topical Solution, 10% [Submission Date: 20 December 2013]

The Microbial Limits specification for Efinaconazole Topical Solution, 10% is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Efinaconazole Topical Solution, 10% is for administration directly to the nail, to the skin folds surrounding the nail, and to any accessible skin of the nail bed for the treatment of onychomycosis.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

MEMORANDUM

Table 1 – Microbial Limits Specifications

Test	Acceptance Criteria
Total Aerobic Microbial Count (USP <61>)	NMT (b) (4) CFU/g
Total Yeast and Mold Count (USP <61>)	NMT (b) (4) CFU/g
<i>S. aureus</i> (USP <62>)	Absent
<i>P. aeruginosa</i> (USP<62>)	Absent

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will not be tested for Microbial Limits as part of the post-approval stability protocol. The drug product contains (b) (4) Ethanol and (b) (4) water and is therefore unlikely to support microbial growth. The drug product was also tested for antimicrobial effectiveness according to USP <51> and met the acceptance criteria for a topical drug product.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol and the drug product formulation is appropriate for a multiple dose topical drug product.

END

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/s/

BRYAN S RILEY
01/13/2014

STEPHEN E LANGILLE
01/13/2014

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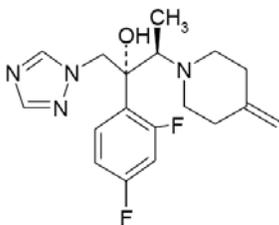
Date Received by CDER: 26 July 2012
Date Assigned: 17 August 2012
Date Review Completed: 28 February 2013
Reviewer: Kerry Snow MS, MT(ASCP)

APPLICANT

Dow Pharmaceutical Sciences, Inc.
1330 Redwood Way
Petaluma, CA 94954-7121
Barry M. Calvarese, MS
Vice President
Regulatory and Clinical Affairs

DRUG PRODUCT NAME

Proprietary name: (b) (4)
Established name: Efinaconazole Solution, 10%
Non-proprietary name: IDP-108 Topical Solution or KP-103 Topical Solution
Chemical name: C₁₈H₂₂F₂N₄O
Molecular formula: (2R,3R, 3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol
Molecular weight: 348.39
Chemical structure:



PROPOSED INDICATION

Treatment of (b) (4) onychomycosis of the toenails

PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION

Form: liquid
Strength: 10%
Route of Administration: topical

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DISPENSED

Rx

RELATED DOCUMENTS

none

REMARKS

The Applicant has submitted a New Drug Application for (b) (4) (efinaconazole) Solution 10% for the once daily treatment of onychomycosis (tinea unguium).

CONCLUSIONS

From a clinical microbiology perspective, the Application is approvable, provided that changes are made to the proposed product labeling, as described below.

PROPOSED LABEL

The Agency recommends the following changes to the proposed label:

1. Strike discussion of (b) (4) from the Mechanism of Action section. Studies performed to evaluate (b) (4) were inconclusive (b) (4) and no clinical relevance of this finding has been established.

2. Delete (b) (4)

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12.4 Microbiology

Mechanism of Action

Efinaconazole is [REDACTED] (b) (4). Efinaconazole inhibits fungal lanosterol 14 α -demethylase involved [REDACTED] (b) (4)

Activity In Vitro and In Vivo

Efinaconazole has been shown to be active against isolates of the following microorganisms, both *in vitro* and in clinical infections. Efinaconazole exhibits *in vitro* minimum inhibitory concentrations (MICs) of 0.06 μ g/mL or less against most [REDACTED] (b) (4) isolates of the following microorganisms:

Trichophyton mentagrophytes

Trichophyton rubrum

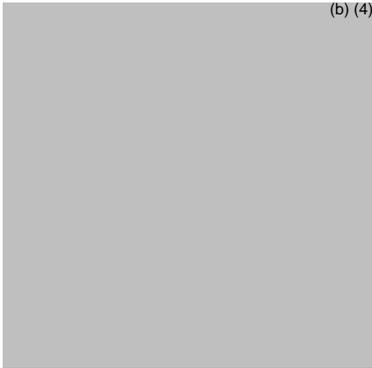
[REDACTED] (b) (4)

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(b) (4)



(b) (4)



(b) (4)



Efinaconazole drug resistance development was studied *in vitro* against *T. mentagrophytes*, *T. rubrum* and *C. albicans*. Serial passage of fungal cultures in the presence of sub-growth inhibitory concentrations of efinaconazole increased the MIC by up to 4-fold, (b) (4)
 The clinical significance of these *in vitro* results is unknown.

(b) (4)



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INTRODUCTION

Onychomycosis is a common fungal infection, most frequently caused by two genera of filamentous fungi (*Trichophyton* sp and *Epidermophyton* sp). *Candida* species are occasionally associated with nail infections in patients with chronic mucocutaneous candidiasis [Gorbach 2004]. Other filamentous fungi (non-dermatophytes) are isolated in rare instances, as the etiologic agents of nail disease [Murray 2003]. There are three types of true dermatophyte infection: 1) distal subungual onychomycosis, 2) proximal subungual onychomycosis, and 3) superficial white onychomycosis. Distal subungual onychomycosis (fungal infection originating from the distal portion of the nail and/or nail bed) is the most commonly diagnosed form of the disease.

Onychomycosis is diagnosed by physical examination, in combination with laboratory findings. Recent guidelines suggest that microscopic examination and culture of subungual debris increase the sensitivity and specificity of diagnosis, and that laboratory results are particularly important when systemic therapy is considered [Drake 1996].

Up to 25% of patients with onychomycosis can be categorized as poor responders or non-responders to topical and/or systemic treatment [Scher 2003]. Although most dermatophyte infections are restricted to the keratinized tissues that are derived from the skin (skin, hair, and nails), significant morbidity is associated with the infection, spread to surrounding tissues is frequent [Szepietowski 2006], and rare invasive disease (deep dermatophyte infection) may occur. Currently available topical therapy is usually inadequate for the successful treatment of nail infections. Oral treatment options for onychomycosis include griseofulvin, terbinafine, itraconazole, and fluconazole [Mandell 2005]. Systemic antifungal therapy, however, is associated with a variety of adverse effects (e.g. hepatotoxicity, congestive heart failure) and the extended time of treatment presents a compliance problem for some patients. Recent evidence suggests a 25 to 30% relapse rate for onychomycosis of the toenail, when treated with either oral terbinafine or oral itraconazole [de Berker 2009].

(b) (4) (Efinaconazole Solution, 10%) is a novel triazole antifungal developed as a topical treatment for onychomycosis. Investigations have demonstrated a lower affinity of IDP-108 for keratin than currently marketed triazole antifungals. This property purportedly allows for greater mobility across the nail plate, and provides the principle rationale for development of the drug.

MECHANISM OF ACTION

The azole-based antimycotic agents appear to target the fungal heme proteins that cocatalyze 14 α -demethylase, a P450 enzyme necessary for the conversion of lanosterol to ergosterol [Ghannoum 1999]. The inhibition of 14 α -demethylase results in the depletion of the ergosterols that are required for the maintenance of fungal cell wall integrity, and in the buildup of ergosterol precursors. Evidence suggests that this depletion results in increased

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cell permeability, with leakage of cell contents. Azoles may affect mammalian cholesterol biosynthesis, but this has only been demonstrated at very high dosages [Balkis 2002].

The Applicant has submitted a study report (Study P090302) from a recent investigation of the mechanism of antifungal action of efinaconazole (KP-103). In this study, researchers measured the effect of efinaconazole on ergosterol synthesis in isolates of *T. mentagrophytes*, by comparing the concentration of [1,2-14C]-sodium acetate in sterol fractions. Results indicated that both efinaconazole and control (itraconazole) decreased the labeled sterols in ergosterol fractions (with concomitant increases in labeled sterol in the lanosterol fraction), in a concentration-dependent manner, when tested at sub-inhibitory concentrations against isolates of *T. mentagrophytes*. These results suggest a mechanism of action in common with that proposed for azole antifungals (described above).

REVIEWER COMMENTS

The Applicant has submitted a study report that supports a mechanism of action similar to other agents described in the azole class of antifungal agents, by correlation of increased antifungal activity in isolates of *T. mentagrophytes* with an efinaconazole-concentration-dependent decrease in ergosterol concentration in the fungal cell membrane sterol fractions.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The in vitro antifungal activity of efinaconazole has been investigated in several studies. Study 07-42 was performed at the (b) (4) in 2010. Minimum inhibitory concentrations (MICs) were determined using methods approved by CLSI (M38A2). The investigators tested 118 clinical isolates, including 69 isolates of *T. rubrum* (25 collected in the U.S.) and 49 isolates of *T. mentagrophytes* (25 collected in the U.S.). Table 1 summarizes the data for this study. Efinaconazole MIC values were lower against all both species than the MIC values of the comparator (itraconazole), and the highest MIC noted was 0.12 mcg/mL, observed in 3 isolates of *T. mentagrophytes* (1 collected in the U.S. and 2 collected in Japan).

Table 1: Antifungal activity against *T. rubrum* and *T. mentagrophytes*

MIC	Species	Test article	Source		
			U.S.	Mexico	Japan
MIC ₉₀ (µg/mL)	<i>T. rubrum</i> (n = 69)	Efinaconazole	0.03	0.015	0.06
		Itraconazole	0.25	0.25	0.25
	<i>T. mentagrophytes</i> (n = 49)	Efinaconazole	0.06	NA	0.06
		Itraconazole	0.5	NA	1
MIC range (µg/mL)	<i>T. rubrum</i>	Efinaconazole	0.004-0.03	0.004-0.03	0.004-0.06
		Itraconazole	0.03-0.25	0.03-0.25	0.06-0.25
	<i>T. mentagrophytes</i>	Efinaconazole	0.004-0.12	0.015-0.03	0.004-0.12
		Itraconazole	0.03-1	0.25-1	0.25-1

NA = not applicable
Source: Study 07-42

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Source: This submission, Module 2.7.2.4, page 32

Study DSIN-7001-A6HP-27-11 was performed at the (b) (4) in 2012.

Investigators compared the in vitro activity of efinaconazole, itraconazole, ciclopirox, amorolfine, and terbinafine against clinical isolates of *T. rubrum* (n=130) and *T. mentagrophytes* (n=129), using susceptibility testing methods approved by CLSI (M38-A2). The results of the study are summarized in Tables 2 and 3. Efinaconazole, in this study, was more active, in vitro, against all tested isolates of *T. rubrum*, as determined by the calculated MIC₉₀. In vitro efficacy against isolates of *T. mentagrophytes* was equal to or better than all comparators.

Table 2: *Trichophyton rubrum* minimal inhibitory concentration (MIC) data summary

Source	MIC (µg/mL)	EFIN	TERB	CIC	ITRA	AMO
North America (n=105)	Range	0.001-0.015	0.004-0.06	0.03-0.5	0.015-0.06	0.004-0.015
	MIC ₅₀	0.002	0.008	0.125	0.03	0.008
	MIC ₉₀	0.008	0.03	0.25	0.06	0.015
	Geometric mean	0.003	0.009	0.108	0.036	0.008
Japan (n=25)	Range	0.001-0.015	0.004-0.015	0.03-0.25	0.015-0.125	0.004-0.015
	MIC ₅₀	0.004	0.008	0.06	0.03	0.008
	MIC ₉₀	0.008	0.015	0.125	0.06	0.015
	Geometric mean	0.004	0.008	0.079	0.038	0.008
All (n=130)	Range	0.001-0.015	0.004-0.06	0.03-0.5	0.015-0.125	0.004-0.015
	MIC ₅₀	0.002	0.008	0.125	0.03	0.008
	MIC ₉₀	0.008	0.015	0.25	0.06	0.015
	Geometric mean	0.003	0.009	0.101	0.037	0.008

EFIN = efinaconazole; ITRA = itraconazole; AMO = amorolfine; CIC = ciclopirox; TERB = terbinafine

Source: Study DSIN-7001-A6HP-27-11

Source: This submission, Module 2.7.2.4, page 33

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Table 3: *Trichophyton mentagrophytes* minimal inhibitory concentration (MIC) data summary

Source	MIC (µg/mL)	EFIN	TERB	CIC	ITRA	AMO
North America (n=104)	Range	0.001-0.015	0.002-0.03	0.03-0.5	0.03-0.25	0.004-0.03
	MIC ₅₀	0.008	0.008	0.06	0.06	0.008
	MIC ₉₀	0.015	0.015	0.25	0.125	0.015
	Geometric mean	0.0056	0.0087	0.088	0.063	0.0086
Japan (n=25)	Range	0.002-0.03	0.004-0.5	0.03-0.5	0.03-0.25	0.004-0.06
	MIC ₅₀	0.004	0.015	0.125	0.06	0.008
	MIC ₉₀	0.015	0.03	0.25	0.125	0.015
	Geometric mean	0.0052	0.014	0.126	0.0062	0.009
All (n=129)	Range	0.001-0.03	0.004-0.5	0.03-0.5	0.03-0.25	0.004-0.06
	MIC ₅₀	0.004	0.008	0.06	0.06	0.008
	MIC ₉₀	0.015	0.03	0.25	0.125	0.015
	Geometric mean	0.005	0.010	0.094	0.063	0.009

EFIN = efinaconazole; ITRA = itraconazole; AMO = amorolfine; CIC = ciclopirox; TERB = terbinafine

Source: Study DSN-7001-A6HP-27-11

Source: This submission, Module 2.7.2.4, page 34

The Applicant has reported results from a study conducted in Japan (Study P080101), where 27 clinical isolates of *T. mentagrophytes*, collected in Japan, were tested against efinaconazole and comparators (clotrimazole, neticonazole, lanoconazole, butenafine, terbinafine, ciclopirox, itraconazole, and amorolfine). Investigators employed susceptibility test methods approved by CLSI (M38-A). The calculated MIC₉₀ of efinaconazole against the tested isolates was 0.13 mcg/mL (slightly more active than all comparators except for lanoconazole, butenafine, and terbinafine). The results of the study are summarized in Table 4.

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Table 4: MIC values of KP-103 (efinaconazole) and commercially available antifungal agents for 27 *T. mentagrophytes* clinical isolates

Test substances	MIC (µg/mL)		
	Range	MIC ₅₀	MIC ₉₀
KP-103	0.016 - 0.13	0.031	0.13
ITCZ	0.063 - 1.0	0.25	0.50
CTZ	0.031 - 0.50	0.063	0.25
NCZ	0.031 - 0.25	0.063	0.13
LCZ	0.001 - 0.0039	0.0020	0.0039
AMF	0.031 - >1.0	0.25	0.50
BTF	0.016 - 0.25	0.031	0.063
TBF	0.0078 - 0.13	0.016	0.031
CPX	0.50	0.50	0.50

ITCZ: itraconazole, CTZ: clotrimazole, NCZ: neticonazole, LCZ: lanoconazole,

AMF: amorolfine, TBF: terbinafine, CPX: ciclopirox.

Source: Table 1; Study P080101 study report

In two identically designed studies, researchers in Japan investigated the minimum inhibitory concentration and minimum fungicidal concentration (MIC/MFC) of efinaconazole against 39 isolates of *T. rubrum* (Study KP950631) and 28 isolates of *T. mentagrophytes* (Study KP950630). The studies, conducted in 1996 at Kaken Pharmaceutical Co, Ltd (Japan), did not employ methods approved by CLSI, but complete study reports including details of methodology have been provided. Susceptibility testing was performed by the micro-dilution method, using 96-well plates, which were incubated at 30°C for 7 days following inoculation. Following determination of the MIC (“...the minimum concentration of the test compound at which the growth of the microorganisms was grossly inhibited...”), aliquots were removed from the well corresponding to the MIC and the next 3 2-fold dilutions, and were plated to determine the fungicidal concentration (“...concentration at which more than 98% of the inoculated microorganisms are killed.”). In these studies, the efinaconazole MIC₉₀ and MFC₉₀ were both 0.5 mcg/mL for *T. mentagrophytes*. For isolates of *T. rubrum*, the efinaconazole MIC₉₀ was 0.25 mcg/mL and the MFC₉₀ was 0.50 mcg/mL. The study results suggest that efinaconazole demonstrates fungicidal activity against these commonly isolated dermatophytes.

In Study DSIN-7001-A6HP-31-11, conducted the [REDACTED] (b) (4) [REDACTED] in 2012, researchers investigated the in vitro antifungal activity of efinaconazole against 105 clinical isolates of *Candida albicans*. The laboratory employed yeast susceptibility testing methods approved by CLSI (M27-A3). The results of the study are summarized in Table 5. The efinaconazole MIC₉₀ value was lower than those of all comparators (terbinafine, ciclopirox, amorolfine, and itraconazole)

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Table 5: *Candida albicans* minimal inhibitory concentration (MIC) data summary

MIC (µg/mL)	EFIN	TERB	CIC	ITRA	AMO
24 hours					
Range	≤ 0.0005->0.25	0.06->16	0.06-0.5	≤ 0.004->2	≤ 0.03-0.5
MIC ₅₀	0.001	1	0.125	0.008	0.03
MIC ₉₀	0.06	4	0.25	0.125	0.125
Geometric mean	0.0029	1.409	0.151	0.014	0.041
48 hours					
Range	≤ 0.0005->0.25	0.125->16	0.06-0.5	≤ 0.004->2	≤ 0.03-8
MIC ₅₀	0.004	4	0.25	0.015	0.03
MIC ₉₀	>0.25	>16	0.5	>2	1
Geometric mean	0.0079	6.873	0.248	0.039	0.091

EFIN = efinaconazole; ITRA = itraconazole; AMO = amorolfine; CIC = ciclopirox; TERB = terbinafine
n = 105
Source: Study DSIN-7001-A6HP-31-11

The Applicant has included a table summarizing the in vitro antifungal activity of efinaconazole against a variety of “other causative pathogens of onychomycosis in humans” (Table 6). The data included in the table was culled from two similarly-designed studies (Study P100301 and Study P100303), performed at Kaken Pharmaceutical Co. (Japan) in 2010. In these studies, researchers employed methods approved by CLSI (M38-A2), testing small numbers of each species by broth microdilution techniques. For the purposes of this submission, no single species (i.e. those species listed in Table 6) was tested in numbers sufficient to permit meaningful microbiologic analysis. In addition, no rationale was provided to support the contention that any single species listed in Table 6 is a significant pathogen typically associated with onychomycosis.

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Table 6: “Efinaconazole antifungal activity in onychomycosis causative pathogens”

Species (Study No.)	No. of Strains Tested	MIC (µg/mL)	Test Article				
			EFIN	AMO	CIC	TERB	ITRA
Dermatophytid Molds							
<i>Trichophyton tonsurans</i> (P100301)	1	MIC	0.016	0.25	0.25	0.016	0.13
<i>Trichophyton verrucosum</i> (P100301)	1	MIC	0.0039	0.25	0.13	0.016	0.016
<i>Trichophyton schoenleinii</i> (P100301)	1	MIC	0.0039	0.016	0.25	0.0039	0.13
<i>Microsporum canis</i> (P100301)	2	Geometric mean	0.18	>4	0.25	0.13	0.35
		Range	0.13-0.25	>4	0.25	0.063-0.25	0.25-0.50
<i>Epidermophyton floccosum</i> (P100301)	3	Geometric mean	≤ 0.005	0.16	0.31	0.039	0.08
		Range	≤ 0.002-0.0078	0.13-0.25	0.25-0.50	0.031-0.063	0.063-0.13
Nondermatophytid Molds							
<i>Scopulariopsis brevicaulis</i> (P100303)	4	Geometric mean	0.25	0.09	0.59	1.0	>4
		Range	0.13-0.50	0.063-0.13	0.50-1	0.50-2.0	>4
<i>Acremonium potronii</i> (P100303)	3	Geometric mean	0.31	0.26	0.25	0.25	>2.5
		Range	0.25-0.50	0.13-1	0.13-0.50	0.13-0.50	1->4
<i>Acremonium sclerotigenum</i> (P100303)	2	Geometric mean	0.18	1	1.4	0.09	>4
		Range	0.13-0.25	1	1-2	0.063-0.13	>4
<i>Fusarium oxysporum</i> (P100303)	3	Geometric mean	1	>4	1	2.5	>4
		Range	0.50-2	>4	1	1-4	>4
<i>Fusarium solani</i> (P100303)	1	MIC	0.50	>4	>4	4	>4
Yeasts							
<i>Candida parapsilosis</i> (P090303)	13	Geometric mean	≤ 0.0046	0.56	0.22	0.28	0.13
		Range	≤ 0.002-0.016	0.13-4	0.13-0.50	0.13-1	0.063-0.25
		MIC ₅₀	0.0039	0.50	0.25	0.25	0.13
		MIC ₉₀	0.016	2	0.50	0.50	0.25
<i>Candida krusei</i> (P090303)	10	Geometric mean	0.024	0.27	0.21	>8	0.38
		Range	0.0078-0.063	0.13-0.50	0.13-0.25	>8	0.13-0.50
		MIC ₅₀	0.016	0.25	0.25	>8	0.50
		MIC ₉₀	0.063	0.50	0.25	>8	0.50
<i>Candida tropicalis</i> (P090303)	10	Geometric mean	0.014	Not calculated	0.50	>8	0.31
		Range	0.0078-0.063	0.016->8	0.50	>8	0.063-0.50
		MIC ₅₀	0.016	0.50	0.50	>8	0.25
		MIC ₉₀	0.016	>8	0.50	>8	0.50

EFIN = efinaconazole; ITRA = itraconazole; AMO = amorolfine; CIC = ciclopirox; TERB = terbinafine
Geometric mean and range calculated for species with at least 2 isolates tested. MIC₅₀ and MIC₉₀ calculated for species with at least 10 isolates

Source: Module 2.7.2; Table 17, this submission

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In Study P110302, conducted at Kaken Pharmaceuticals (Japan) in 2011, investigators conducted in vitro susceptibility tests against isolates of *T. mentagrophytes*, *T. rubrum*, and *C. albicans*, using three efinaconazole stereoisomers, five metabolites, two impurities, and three degradation products, all identified as efinaconazole-related compounds. The susceptibility testing was performed according to methods approved by CLSI (M38-A2 and M27-A3). The results of the study are summarized in Table 7. In vitro activity of the tested compounds varied widely and all displayed activity significantly lower than that of efinaconazole. The Applicant concluded, based on the result of this study, that "...these compounds may not contribute to the therapeutic effects of KP-103."

Table 7: MICs of KP-103, its metabolites, stereoisomers, impurities, degradation products, and reference compounds (itraconazole and ciclopirox olamine)

Species	Kaken's stock strain No.	MIC (µg/mL)										(b) (4)		
		KP-103	H1	H2	H3	H4	H5	Itaconazole (2S, 3S)	Itaconazole (2R, 3S)	Itaconazole (2S, 3R)				
<i>Trichophyton mentagrophytes</i>	KD-1010	0.0025	>64	8.0	64	2.0	0.063	2.0	0.25	0.50			0.016	0.13
	KD-1012	0.0078	>64	0.25	>64	0.50	0.016	4.0	0.50	8.0			0.063	0.13
	KD-1022	0.0020	>64	1.0	64	1.0	0.016	0.50	0.13	0.25			0.031	0.13
	KD-1024	0.0020	>64	2.0	>64	2.0	0.031	0.25	0.063	0.50			0.0078	0.063
	KD-1029	0.0039	>64	1.0	64	0.25	0.0078	0.25	0.25	2.0			0.063	0.13
	KD-1031 (Reference strain)	0.016	>64	>16	>64	8.0	0.13	2.0	0.25	4.0			0.063	0.13
<i>Trichophyton rubrum</i>	KD-1104	0.0020	>64	2.0	>64	0.50	0.031	0.50	0.13	1.0			0.031	0.25
	KD-1108	0.0020	>64	1.0	>64	2.0	0.063	1.0	0.13	1.0			0.063	0.13
	KD-1121	0.0039	>64	2.0	>64	2.0	0.063	2.0	0.13	1.0			0.13	0.13
	KD-1126	0.0039	>64	2.0	>64	4.0	0.063	1.0	0.13	1.0			0.063	0.13
	KD-1132	0.0039	>64	1.0	>64	2.0	0.063	1.0	0.13	2.0			0.13	0.13
	KD-1137 (Reference strain)	0.0039	>64	1.0	>64	2.0	0.063	1.0	0.13	1.0			0.13	0.13
<i>Candida albicans</i>	KC-1001	0.0010	>64	0.50	>64	0.50	0.031	0.13	0.031	0.50			0.0078	0.13
	KC-1006	0.0010	>64	0.50	>64	0.50	0.031	0.13	0.063	0.50			0.0078	0.13
	KC-1007	0.0010	>64	0.50	>64	1.0	0.031	0.063	0.031	0.50			0.0078	0.063
	KC-1009	0.00650	>64	0.25	64	0.50	0.016	0.063	0.031	0.25			0.0039	0.13
	KC-1010	0.0020	>64	1.0	>64	1.0	0.063	0.13	0.063	1.0			0.0078	<0.031
<i>Candida parapsilosis</i> (Quality control strain)	KC-145	0.0078	>64	4.0	64	4.0	0.13	2.0	1.0	4.0			0.13	0.13

Source: Study P110302, Appendix Table

In a study performed by (b) (4) in 2012, investigators tested efinaconazole (identified in the study report as S-32282) at various concentrations in an in vitro *T. rubrum*-infected nail model. In this model, human nail sections are infected on the underside with actively growing cultures of the dermatophyte, placed on specially designed cells (ChubTur®), and incubated at 25°C for 14 days. The nails were then treated "on the dorsal surface with a single 1 µL of efinaconazole formulated in IDP-108 vehicle at 2.5%, 5%, or 10% w/w (n= 8 cells per treatment) and incubated for another 14 days." In this assay, ATP is measured in the tested nail samples to determine the extend of fungal infection. Baseline ATP levels are defined as those measured in the uninfected nail sample. In addition to this control, an untreated nail was included in the assay. The results of the study are summarized in Table 8. Compared to the infected control, all doses of efinaconazole resulted in greater reduction in ATP levels (without apparent relationship of dose to eradication effect).

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Table 8: “IDP-108 antifungal activity (ATP levels) in an in vitro onychomycosis model

Treatment	Timepoint (Days Post-Infection)	Number of Toenails Evaluated ^a	Mean ATP ± SD (% of 28-Day Infected Control)
IDP-108 10%	28	7	16.9 ± 33.4
IDP-108 5%	28	6	15.6 ± 19.7
IDP-108 2.5%	28	8	19.0 ± 11.3
IDP-108 Vehicle	28	7	40.8 ± 21.2
Infected control	14	8	49.2 ± 24.2
Infected control	28	8	100.0 ± 45.5
Non-infected control	28	3	1.5 ± 1.8

^a Some toenails were excluded from analysis due to misalignment within the cells
Source: Study KKN1001-02R

REVIEWER COMMENTS

The Applicant has submitted study reports that support a claim for in vitro antifungal activity of efinaconazole against isolates of *T. rubrum* and *T. mentagrophytes* (the fungal pathogens included in the proposed indications for this drug). Data from these studies suggest an MIC₉₀ against isolates of *T. rubrum* ranging from 0.0015 – 0.06 mcg/mL, and for an MIC₉₀ against isolates of *T. mentagrophytes* ranging from 0.004 – 0.13 mcg/mL. The highest MIC observed for efinaconazole against any isolate of the two significant species tested (*T. rubrum* and *T. mentagrophytes*) was 0.13 mcg/mL.

RESISTANCE STUDIES

The Applicant has submitted two reports from studies designed to investigate the development of resistance in dermatophytes to efinaconazole.

Study P100304, “Resistance-acquiring test of *Trichophyton rubrum* to KP-103” was performed in 2011 by Kaken Pharmaceutical Co., Ltd (Kyoto, Japan). The investigation was designed as a serial passage study, where 6 isolates of *T. rubrum* were cultured in the presence of sub-inhibitory concentrations of efinaconazole (KP-103) or itraconazole for 12 passages, with MIC values obtained at each step. Susceptibility testing was performed using a “modified CLSI M38-A2 method” (using Sabouraud dextrose broth instead of RPMI 1640 media). Tested drug ranges were 0.0038 – 0.13 mcg/mL for efinaconazole and 0.002 – 1.0 mcg/mL for itraconazole. In this study, investigators noted only two isolates in the efinaconazole group with a MIC increase of 2-fold or higher (with a maximum of a 4-fold increase, from 0.0020 mcg/mL to 0.0078 mcg/mL). The highest efinaconazole MIC observed was 0.031 mcg/mL.

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Table 9: Changes in MIC of KP-103 and ITCZ for *T. rubrum*

Test substance	Test strain	MIC (µg/mL) on each passage number												MIC ratio of passage 12 to 0	
		0 ¹⁾	1	2	3	4	5	6	7	8	9	10	11		12
KP-103	IFM47169	0.0020	0.0039	0.0078	0.016	0.016	0.0078	0.0078	0.0078	0.0039	0.0039	0.0078	0.0078	0.0078	4
	IFM47615	0.016	0.016	0.016	0.031	0.016	0.016	0.031	0.016	0.016	0.016	0.016	0.016	0.031	2
	IFM47622	0.0078	0.0078	0.0078	0.0078	0.0078	0.0078	0.0078	0.0078	0.0039	0.0039	0.0039	0.0039	0.0078	1
	IFM47625	0.0078	0.0039	0.0078	0.016	0.0078	0.0078	0.016	0.0078	0.0078	0.0078	0.0078	0.0078	0.0078	1
	IFM46157	0.0078	0.0039	0.0078	0.0078	0.0039	0.0039	0.0078	0.0039	0.0039	0.0078	0.0078	0.0078	0.0039	1/2
	IFM46244	0.016	0.016	0.016	0.031	0.016	0.016	0.031	0.031	0.016	0.016	0.016	0.016	0.016	1
ITCZ	IFM47169	0.00050	0.0010	0.0010	0.0039	0.0020	0.0010	0.0010	0.00050	0.00050	0.0010	0.0010	0.0010	0.0020	4
	IFM47615	0.0039	0.0039	0.0078	0.031	0.016	0.0078	0.0078	0.016	0.016	0.016	0.016	0.016	0.016	4
	IFM47622	0.0010	0.0020	0.0039	0.0078	0.0039	0.0020	0.0039	0.0020	0.0039	0.016	0.0078	0.016	0.016	16
	IFM47625	0.0039	0.0010	0.0039	0.0078	0.0039	0.0020	0.0020	0.0010	0.0010	0.0020	0.0020	0.0010	0.0020	1/2
	IFM46157	0.0010	0.0010	0.0010	0.0020	0.0010	0.0039	0.0020	0.0020	0.0039	0.0020	0.0010	0.0020	0.0010	1
	IFM46244	0.0078	0.0078	0.0078	0.016	0.016	0.016	0.016	0.016	0.0078	0.0078	0.0039	0.0078	0.0039	1/2

ITCZ: Itraconazole

¹⁾ Passage number 0 : Start of passage

Source: Study P100304, study report

Study KP960608, “In vitro resistance-acquiring test of *T. mentagrophytes* to KP-103 or clotrimazole”, was performed at the Kaken Pharmaceutical Co. Ltd. (Japan) in 1996. The investigators employed a study design similar to the one described above, but tested only one isolate of *T. mentagrophytes* (“KD-04”), over 10 passages. The susceptibility test method employed in the study was not adequately described in the study report. The investigators reported that the MIC of the tested isolates “increased two-fold after 10 passages” (from a baseline of 0.5 mcg/mL) (data not shown).

In Study KP960217, “In vitro resistance-acquiring tests of *C. albicans* to KP-103 or clotrimazole” (Kaken Pharmaceutical Co, Ltd., Japan), investigators studied the development of resistance in an isolate of *C. albicans* using serial passage studies in sub-inhibitory concentrations of efinaconazole or control (clotrimazole). Over 10 passages, the MIC of the test isolate increased only two-fold (data not shown), indicating no significant development of resistance in this pathogen.

REVIEWER COMMENTS

The Applicant has submitted reports from three studies that demonstrate a low potential for the development of resistance in specific fungal pathogens (*T. rubrum*, *T. mentagrophytes*, and *C. albicans*) to efinaconazole. In investigations of *T. rubrum*, one isolate demonstrated a 4-fold MIC increase in serial passage studies (comparable to the comparator, itraconazole), but overall, the increase in MIC values over 10 passages, for the three tested pathogens, was 2-fold or less.

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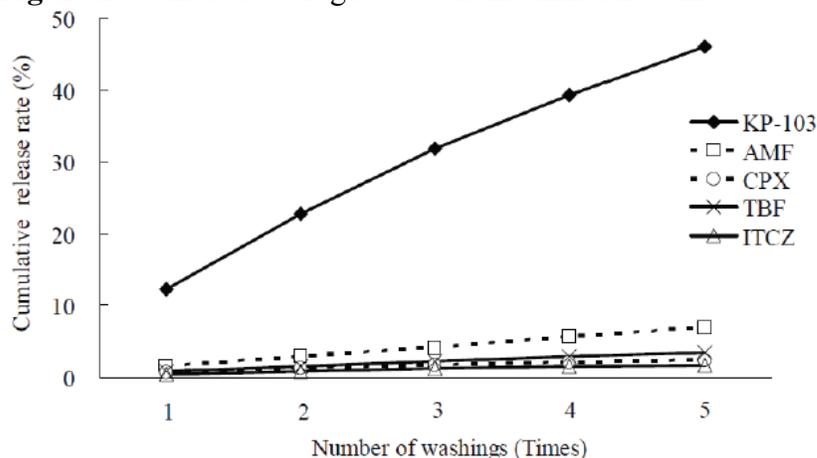
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MISCELLANEOUS STUDIES

Keratin Binding

The Applicant has submitted study reports from a series of experiments designed to investigate the keratin-binding properties of efinaconazole and comparators (Studies M100102 and KP960211), and to describe the effect of such binding on the in vitro antifungal activity of the tested antifungals against a strain of *T. mentagrophytes* (Study KP990205). In Study M100102, the investigators demonstrated that efinaconazole absorption to keratin was less than that seen in the various comparators (e.g. 85.7% absorption for efinaconazole compared to 99.5% absorption for itraconazole), and that the cumulative release of the drug after 5 washes was greater than that observed in the comparators (Figure 1). The results of Study KP960211 (where keratin binding of efinaconazole was compared to that of lanocanazole and butenafine) demonstrated similar absorption properties of the study drug.

Figure 1: Cumulative drug release from animal keratin



KP-103 = efinaconazole; AMF = amorolfine; CPX = ciclopirox; TBF = terbinafine; ITCZ = itraconazole
Each timepoint represents mean of n = 3 replicates
Source: Module 2.7.2; Figure 9, this submission

In an investigation of the effect of keratin binding on the in vitro antifungal activity of efinaconazole, the minimum inhibitory concentration of efinaconazole was less effected by the presence of keratin than either of the tested comparators (amorolfine and terbinafine), although the MICs of all tested drugs were identical against the test isolate. The results of the study are summarized in Table 10.

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Table 10: MICs of KP-103 (efinaconazole) and reference drugs against *T. mentagrophytes* SM-110 in SDB alone and SDB containing 5% keratin

Test material	MIC (µg/mL) for <i>T. mentagrophytes</i> SM-110		Reduction in activity (B/A ratio)
	SDB alone (A)	SDB with 5% keratin (B)	
KP-103	0.2	0.2	1
AMF	0.025	0.2	8
TBF	0.006	0.2	32

SDB: Sabouraud dextrose broth.
Source: Study KP990205

Human Nail Study

The Applicant has submitted a report from a study titled, “A Phase II Dose-Ranging, Safety, and Efficacy Study of IDP-108 Topical Solution vs. Vehicle in Subjects with Mild to Moderate Onychomycosis of the Toenails” (Study Report DPSI-IDP-108-P2-01),

Dose dependent efficacy of efinaconazole against dermatophytes was studied in an in vitro nail model. The investigation, Study KKN1001-02, “Examination of Dose Dependent Efficacy of S-32282 Against an In Vitro Model of Onychomycosis”, was reported in 2012, and performed by (b) (4). In an earlier investigation performed by the same laboratory, a “marked reduction in visible dermatophytes” were recovered from nails treated with 1 µL of both the 5% w/w preparation and the 10% w/w/ preparation of S-22282 (efinaconazole). The researchers also noted a “notable effect” in the placebo arm of the experiment, though, and proposed that the alcohol content of the formulation was contributing to the observed fungicidal activity of all three preparations. In the study described in this submission, 3 drug concentrations were tested (10% w/w, 5% w/w, and 2.5% w/w), and compared to vehicle. The nail infection model (“ChubTur[®] infected nail assay”) was performed using conidial preparations from a fresh isolate of *T. rubrum* (strain designation not provided). Nail section were infected on the underside with the fungal preparation, mounted in the ChubTur[®] cells, and the cells were incubated for 14 days. Nails were then treated with the experimental solutions or were left untreated as controls. Fourteen days after dosing, the nails were removed from the cells for ATP analysis, as an indicator of viable fungi in the nail specimen. The results of the study are summarized in Table 11. Statistical analysis (non parametric Tukey’s test at a 95% confidence level for all test samples and 28 day infected control) was performed, and the investigators reported “a significant (p<0.05) increase in organism kill (indicated by a decrease in % recovery of ATP) following application of all S-32282 formulation in comparison with the t=28 day infected control, whereas no significant difference (p>0.5) was observed between the vehicle and the t=28 day infected control. The 10% formulation showed the highest complete kill rate of 42.9% (3/7 nails) in the actives, whereas the vehicle showed no complete kill.”

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Table 11: IDP-108 antifungal activity (ATP levels) in an in vitro onychomycosis model

Treatment	Timepoint (Days Post-Infection)	Number of Toenails Evaluated ^a	Mean ATP ± SD (% of 28-Day Infected Control)
IDP-108 10%	28	7	16.9 ± 33.4
IDP-108 5%	28	6	15.6 ± 19.7
IDP-108 2.5%	28	8	19.0 ± 11.3
IDP-108 Vehicle	28	7	40.8 ± 21.2
Infected control	14	8	49.2 ± 24.2
Infected control	28	8	100.0 ± 45.5
Non-infected control	28	3	1.5 ± 1.8

^a Some toenails were excluded from analysis due to misalignment within the cells

Source: Study KKN1001-02R

REVIEWER COMMENTS

The Applicant has submitted study data that suggests that efinaconazole is approximately 10% less keratin-bound than that observed in comparators (efinaconazole, amorolfine, terbinafine, and itraconazole), and that the drug is more completely released after several washings, compared to those same antifungals. A similar study demonstrated that the in vitro antifungal activity of efinaconazole was less affected by keratin binding than was the activity of comparators, when tested against a single isolate of *T. mentagrophytes* (the MIC, however, of all three tested drugs were identical when incubated in the presence of keratin).

In an in vitro human toenail model of onychomycosis, efinaconazole was more active than vehicle in reducing the burden of *Trichophyton rubrum* in infected nails, with similar activity observed at the three tested drug concentrations (2.5%, 5%, and 10%).

ANIMAL AND HUMAN STUDIES

ANIMAL MODELS OF INFECTION

The Applicant has submitted a study report for an investigation performed to evaluate the efficacy of efinaconazole (KP-103) in an animal model of infection. Study NP10018, “Examination of therapeutic effects of topically applied KP-103 clinical solution in a guinea pig tinea unguium model”, was performed at the Kaken Pharmaceutical Co., Ltd. facility (Japan) in 2012. In this study, groups of animals (Table 10) were infected with *T. mentagrophytes* by inoculation to the plantar and interdigital skin, with 28 days of incubation following the inoculation procedure. Treatment occurred on day 29 of the study (the treatment groups are summarized in Table 10). *T. rubrum* is a more common cause of onychomycosis and tinea pedis in humans, *T. mentagrophytes* isolates were used in this study because of the demonstrated success of the animal model that employed this pathogen. No comparable model of onychomycosis was described in the submission, although the Applicant has submitted data demonstrating nail penetration by the antifungal (reviewed above).

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Table 10: Study NP10018, animal test groups

Group	Infection	Administration	Number of animals	Number of feet (number of cases)
28-day administration				
Infected control	Present	Absent	3	6
Vehicle	Present	Nail application	4	8
3% KP-103 clinical solution	Present	Nail application	4	8
10% KP-103 clinical solution	Present	Nail application	4	8
5% AMF nail lacquer	Present	Nail application	4	8
8% CPX nail lacquer	Present	Nail application	4	8
Oral TBF preparation	Present	Oral	4	8
Oral ITCZ preparation	Present	Oral	4	8
14-day administration				
Infected control.	Present	Absent	2	4
10% KP-103 clinical solution	Present	Nail application	4	8

Source: Study report, Study NP10018

KP-103 (efinaconazole), vehicle, and CPX lacquer were applied topically once daily for 28 days; AMF lacquer was applied topically once a week (total 4 times); TBF and ITCZ were administered orally once daily for 8 days at 20 mg/kg

The results of the study are summarized in Table 11. Both the 3% and 10% efinaconazole preparations resulted in an approximate 2 log₁₀ decrease in colony counts, compared to untreated controls. There was no significant difference between the two results. Investigators also noted an approximate 1 log₁₀ decrease in colony counts in animals treated with efinaconazole vehicle, compared to untreated controls. In this model, efinaconazole topical treatment (at both strengths) was more efficacious than oral treatment with either terbinafine (20 mg/kg, PO) or itraconazole (20 mg/kg, PO), and more efficacious than topical treatment with either 5% amorolfine (Loceryl[®]) or 8% ciclopirox.

Table 11: Fungal burden in guinea pig tinea unguium model after treatment with IDP-108 and reference topical and oral drugs

Post-Infection Timepoint (Days)	Group	Log CFU in Nails/Foot (Mean ± SD)
28	Untreated Infection Control	4.97±0.46
	Terbinafine (20 mg/kg, PO)	4.05±0.35**
	Itraconazole (20 mg/kg, PO)	3.99±0.44***
	IDP-108 Vehicle	3.87±0.52*
	3% efinaconazole in IDP-108 Vehicle	2.41±0.76***, ††, ††
	10% efinaconazole (IDP-108)	2.51±0.78***, ††, ††
	Loceryl	3.77±0.38*
	Ciclopirox Topical Solution	3.07±0.74***
14	Untreated Infection Control	4.64±0.20
	10% efinaconazole (IDP-108)	3.68±0.40**

* p<0.05, ** p<0.01, *** p<0.001 compared to corresponding untreated infection control

†† p<0.01, ††† p<0.001 compared to IDP-108 vehicle control

‡‡ p<0.01 compared to Loceryl

Source: Study NP10018

Source: This submission, module 2.7.2 page 51

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In a second guinea pig tinea unguium study (Study KP990206) investigators reported similar efficacy compared to topically applied terbinafine (1%), oral terbinafine (40 mg/kg/day), and topical amorolfine (1%). The Applicant has also summarized data from a guinea pig tinea pedis model and a guinea pig tinea corporis model (study reports not provided), and concluded that [REDACTED] (b) (4)

REVIEWER COMMENTS

The Applicant has submitted studies that demonstrate the efficacy of efinaconazole (3% and 10%) in a guinea pig model of onychomycosis. The efinaconazole preparations were more efficacious than all tested comparators. Of note, the efinaconazole vehicle also decreased fungal burden in this model by approximately 1 log₁₀ viable fungal cells.

HUMAN PHARMACOLOGIC STUDIES

The Applicant has reported four Phase 1 studies (pharmacokinetic and systemic exposure studies), and one Phase 2 study (safety and efficacy), in addition to the two Phase 3 studies conducted to support the Application. Discussions of the Phase 1 studies are not included in this review.

PHASE 2 CLINICAL STUDY

The Applicant has included a summary of a Phase 2 clinical study (Study DPSI-IDP-108-P2-01) that was conducted to investigate the safety and efficacy of IDP-108 (efinaconazole). The study was designed as a multicenter, randomized, double-blind, vehicle controlled, parallel-group study. The study enrolled 135 adult subjects who were randomized 2:2:2:1 to receive the original formulation of IDP-108 with semi-inclusion, IDP-108, IDP-108 5%, or vehicle. Subjects applied the test article to their toenails once daily for 36 weeks. Study visits included a baseline visit (pre-treatment), at Weeks 4, 8, 12, and 24 (intra-dosing assessments), at Week 36, and a 30-day post-treatment follow-up.

Efficacy variables included:

- Treatment success assessed without Blenclerm tape at Weeks 24, 36, and the 30-day post-treatment follow-up visit
Treatment Success was defined as a “complete cure”, which included an affected target toenail area of 0% and mycological cure (a negative outcome in the KOH examination, and a negative fungal culture assessment). The determination of treatment success was based on the affected target toenail area as assessed, individually, with and without Blenclerm tape. (Note that this same variable [without Blenclerm tape] was evaluated in the primary efficacy analysis for the Phase 3 studies; in those studies, the variable was named “Complete Cure”.)
- Clinical efficacy assessed without Blenclerm tape at Weeks 8, 16, 24, 28, 32, 36, and the 30-day post-treatment follow-up visit

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Clinical Efficacy was defined as an affected target toenail area of less than 20%. The determination of clinical efficacy was based on an affected target toenail area as assessed, individually, with and without Blenderm tape.

- Effective treatment assessed without Blenderm tape at Weeks 24, 36, and the 30-day post-treatment follow-up visit

Effective Treatment was defined as a mycologic cure and either an affected target toenail area of 0% or more than 3 mm growth from baseline in the unaffected target toenail. The determination of effective treatment was based on an unaffected target toenail area as assessed, individually, with and without Blenderm tape.

- Mycologic cure at Weeks 12, 24, 36, and the 30-day post-treatment follow-up visit
- Mycologic Cure* was defined as a negative KOH examination and a negative fungal culture assessment of the target toenail.
- KOH examination outcomes at Weeks 12, 24, 36, and the 30-day post-treatment follow-up visit
 - Fungal culture findings at Weeks 12, 24, 36, and the 30-day post-treatment follow-up visit
 - Change from baseline in the percent of the affected target toenail area assessed without Blenderm tape at Weeks 8, 16, 24, 28, 32, 36, and the 30-day post-treatment follow-up visit
 - Change from baseline in the unaffected target toenail measurement assessed without Blenderm tape at Weeks 8, 16, 24, 28, 32, 36, and the 30-day post-treatment follow-up visit
 - IGA of non-target toenails at Weeks 8, 16, 24, 28, 32, 36, and the 30-day post-treatment follow-up visit

Source: this submission; module 2.7.3, page 14

The Applicant reported no statistical difference in the percentage of patients deemed “Treatment Success” at any time point. The percentage of patients achieving “Clinical Efficacy” was significantly greater in the active treatment arms at most time points, including at Week 36 and at the 30-day post-treatment follow-up. Similar results were observed in patients who achieved “Effective Treatment” (statistically significant differences within active arms and between active arms and the placebo arm). With regard to mycological assessments, there were no statistically significant differences in either “Mycological Cure” or negative KOH results at any time point. A statistically significant difference in culture negativity between active arms (IDP-108 with semi-occlusion and IDP-108 5%) and the placebo arm was observed at the later study visits (Week 12 through the 30-day post-treatment follow-up visit).

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PHASE 3 CLINICAL STUDIES

The Applicant has submitted reports and summaries from two identically designed and conducted Phase 3 clinical studies. Study DPSI-IDP-108-01 and DPSI-IDP-108-P3-02 were “multicenter, randomized, double-blind, vehicle controlled, parallel group studies designed to evaluate the safety and efficacy of a once daily topical application of IDP-108 relative to Vehicle in the treatment of mild to moderate onychomycosis of the toenails.” Details of the two individual studies are discussed below. In both studies, patients were randomized 3:1 to efinaconazole 10% or vehicle. Patients were instructed to apply the test article once daily at bedtime, and were seen at 15 study visits (Screening, Baseline, Treatment (weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48) and Post-Treatment follow-up (week 52)). The primary efficacy endpoint “consisted of a comparison between the percentage of subjects in each treatment group who achieved a Complete Cure (defined as 0% clinical involvement of the target toenail, in addition to both a negative KOH examination and a negative fungal culture of the target toenail) at Week 52 (the four-week post-treatment follow-up visit).

The following efficacy variables were evaluated (Source: this submission, module 2.7.3, page 16):

- *Complete Cure*, which was defined as 0% clinical involvement of the target toenail (toenail was totally clear) in addition to a negative KOH examination and a negative fungal culture of the target toenail sample
- *Clinical Efficacy*, which was defined as an affected target toenail area of less than 10% (when evaluated as a secondary efficacy variable [see the discussion that follows regarding Version 1 of the SAP]) or as an affected target toenail area of less than or equal to 10% (when evaluated as a supportive efficacy variable [see the discussion that follows regarding Version 2 of the SAP])
- *Mycologic Cure*, which was defined as a negative KOH examination and a negative fungal culture of the target toenail sample
- *Unaffected new toenail growth*, which was defined as the change from baseline in the healthy (unaffected) target toenail measurement for the target toenail
- *Complete or Almost Complete Cure*, which was defined as an area less than or equal to 5% of the affected target toenail in addition to a negative KOH examination and a negative fungal culture of the target toenail sample
- *Clear Nail*, which was defined as an affected target toenail area of 0%
- *Almost Clear Nail*, which was defined as an affected target toenail area of less than or equal to 5%

In both Phase 3 studies, specimens (toenail clippings and subungual debris) were collected at the screening visit and at 12-week intervals following that visit. All clinical specimens were tested microscopically (KOH examination) and sent to a reference laboratory for culture (b) (4) Dermatophytes isolated in culture were identified by routine methods. Isolates collected at Visits 1 (screening), 14 (week 48,

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end of therapy), and 15 (week 52, end of study follow-up) were sub-cultured to ensure a pure culture of the specific pathogen, then shipped to a reference laboratory for susceptibility testing (b) (4)

The Applicant has included the complete study report from the reference laboratory (Study DSIN-7001-A6HP-39-11). Susceptibility testing was performed using broth dilution methods approved by CLSI (CLSI M38-A2). Susceptibility testing was not performed on cultures that were determined to be contaminated with other fungi (non-dermatophytes), bacteria, mites, etc. Quality control was performed on each day of susceptibility testing, using the criteria described in Table 12. All QC tests were within acceptable limits (data reported in Study DSIN-7001-A6HP-39-11). Results from MIC testing of reference strains against efinaconazole were within a narrow range (all results were with three doubling dilutions).

Table 12: Quality control acceptance ranges for reference stains as per CLSI M38-A2

Antifungal	Acceptance Range (µg/mL)	
	<i>T. mentagrophytes</i> MYA-4439	<i>T. rubrum</i> MYA-4438
Efinaconazole	Not established	Not established
Ciclopirox	0.5 - 2	0.5 - 2
Itraconazole	0.03 - 0.25	Not established
Terbinafine	0.002 - 0.008	Not established

Source: this submission, Module 2.7.2, page 57

STUDY DPSI-IDP-108-P3-01

Study DPSI-IDP-108-P3-01 was performed in investigational centers in the U.S. (n=34), Japan (n=33), and Canada (n=7). Investigators randomized 656 patients to the active treatment arm and 214 patients to the vehicle arm. The Applicant reported no meaningful differences in baseline characteristics or demographics between the treatment arms. The analysis of the primary endpoint is summarized in Table 13. With regard to the Mycological Cure secondary endpoint, 55.2% of patients randomized to the IDP-108 arm and 16.8% of patients randomized to the vehicle arm had negative microscopy and dermatophyte cultures at the Week 52 Visit (p<0.001).

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Table 13: Analysis of the primary efficacy endpoint at week 52 (ITT subjects, DPSI-IDP-108-P3-01)

Number of subjects	<u>IDP-108</u> 656	<u>Vehicle</u> 214	
<u>Complete Cure at Week 52</u> ^a	<u>IDP-108</u>	<u>Vehicle</u>	<u>P-Value</u>
Success, n (%)	117 (17.8)	7 (3.3)	<0.001 ^b
Failure, n (%)	539 (82.2)	207 (96.7)	

^a A Complete Cure was defined as both 0% clinical involvement of the target toenail (i.e., the toenail was totally clear) in addition to a Mycologic Cure (i.e., a negative potassium hydroxide examination and a negative fungal culture of the target toenail sample).

^b P-value from a Cochran-Mantel-Haenszel test, stratified by analysis center.

Note: The last observation carried forward method was used to impute missing data prior to the analysis.

Source: Table 11-4 in the DPSI-IDP-108-P3-01 Clinical Study Report

Source: this submission, Module 2.7.3, page 37

A total of 1041 fungal isolates were collected at the screening visit. Of these, the reference laboratory tested 875 isolates for susceptibility to efinaconazole and comparators (the remainder were either deemed too contaminated for further analysis or corresponded to study visits that were not relevant for the planned analysis). Tested dermatophyte species included *Trichophyton rubrum* (n = 798), *T. mentagrophytes* (n = 73), and *Epidermophyton floccosum* (n = 4) (Table 14). Approximately 91% of the tested isolates were from Visit 1. The reference laboratory reported “no meaningful differences in MIC between geographical locations and no increase in MIC was noted in specimens collected on Visits 14 or 15 as compared to Visit 1.” Study Report DSIN-7001-A6HP-39-11 includes a complete line list of all susceptibility test results performed on each isolate, as well as a complete record of quality control results.

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Table 14: Number of dermatophyte isolates tested for Study DPSI-108-P3-01

Isolate	Visit	US	Canada	North America	Japan	All
<i>Epidermophyton floccosum</i>	1	3	0	3	1	4
	14	0	0	0	0	0
	15	0	0	0	0	0
	Total	3	0	3	1	4
<i>Trichophyton mentagrophytes</i>	1	14	10	24	46	70
	14	1	0	1	0	1
	15	2	0	2	0	2
	Total	17	10	27	46	73
<i>Trichophyton rubrum</i>	1	408	112	520	206	726
	14	14	3	17	3	20
	15	38	3	41	11	52
	Total	460	118	578	220	798

North America = US + Canada

Source: Study DSIN-7001-A6HP-39-11

Summarized antifungal susceptibility data for the three principle fungal pathogens isolated in Study DPSI-IDP-108-P3-01 are summarized in Tables 15-17.

Table 15: Summary of in vitro susceptibility data for DPSI-IDP-108-P3-01 clinical trial isolates of *Epidermophyton floccosum*

Visit	Country	No. Isolates	No. Isolates Inhibited at Concentration (µg/mL)						MIC (µg/mL)		
			≤0.002	0.004	0.008	0.015	0.03	0.06	Range	MIC ₅₀	MIC ₉₀
1	US	3	1	1	1	0	0	0	≤0.002-0.008	NA	NA
1	Canada	0	0	0	0	0	0	0	NA	NA	NA
1	N. America	3	1	1	1	0	0	0	≤0.002-0.008	NA	NA
1	Japan	1	0	0	0	1	0	0	0.015	NA	NA
1	All	4	1	1	1	1	0	0	≤0.002-0.015	NA	NA
14	US	0	0	0	0	0	0	0	NA	NA	NA
14	Canada	0	0	0	0	0	0	0	NA	NA	NA
14	N. America	0	0	0	0	0	0	0	NA	NA	NA
14	Japan	0	0	0	0	0	0	0	NA	NA	NA
14	All	0	0	0	0	0	0	0	NA	NA	NA
15	US	0	0	0	0	0	0	0	NA	NA	NA
15	Canada	0	0	0	0	0	0	0	NA	NA	NA
15	N. America	0	0	0	0	0	0	0	NA	NA	NA
15	Japan	0	0	0	0	0	0	0	NA	NA	NA
15	All	0	0	0	0	0	0	0	NA	NA	NA

NA = not applicable; no MIC data to determine range or number of isolates <10 so MIC₅₀ and MIC₉₀ were not calculated

Source: Study DSIN-7001-A6HP-39-11

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Table 16: Summary of in vitro susceptibility data for DPSI-IDP-108-P3-01 clinical trial isolates of *Trichophyton mentagrophytes*

Visit	Country	No. Isolates	No. Isolates Inhibited at Concentration (µg/mL)						MIC (µg/mL)		
			≤0.002	0.004	0.008	0.015	0.03	0.06	Range	MIC ₅₀	MIC ₉₀
1	US	14	2	0	7	5	0	0	≤0.002-0.015	0.008	0.015
1	Canada	10	5	1	3	1	0	0	≤0.002-0.015	≤0.002	0.008
1	N. America	24	7	1	10	6	0	0	≤0.002-0.015	0.008	0.015
1	Japan	46	27	10	5	3	0	1	≤0.002-0.06	≤0.002	0.008
1	All	70	34	11	15	9	0	1	≤0.002-0.06	0.004	0.015
14	US	1	0	1	0	0	0	0	0.004	NA	NA
14	Canada	0	0	0	0	0	0	0	NA	NA	NA
14	N. America	1	0	1	0	0	0	0	0.004	NA	NA
14	Japan	0	0	0	0	0	0	0	NA	NA	NA
14	All	1	0	1	0	0	0	0	0.004	NA	NA
15	US	2	2	0	0	0	0	0	≤0.002	NA	NA
15	Canada	0	0	0	0	0	0	0	NA	NA	NA
15	N. America	2	2	0	0	0	0	0	≤0.002	NA	NA
15	Japan	0	0	0	0	0	0	0	NA	NA	NA
15	All	2	2	0	0	0	0	0	≤0.002	NA	NA

NA = not applicable; no MIC data to determine range or number of isolates <10 so MIC₅₀ and MIC₉₀ were not calculated

Source: Study DSIN-7001-A6HP-39-11

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Table 17: Summary of in vitro susceptibility data for DPSI-IDP-108-P3-01 clinical trial isolates of *Trichophyton rubrum*

Visit	Country	No. Isolates	No. Isolates Inhibited at Concentration (µg/mL)						MIC (µg/mL)		
			≤0.002	0.004	0.008	0.015	0.03	0.06	Range	MIC ₅₀	MIC ₉₀
1	US	408	284	58	48	15	3	0	≤0.002-0.03	≤0.002	0.008
1	Canada	112	69	24	13	5	1	0	≤0.002-0.03	≤0.002	0.008
1	N. America	520	353	82	61	20	4	0	≤0.002-0.03	≤0.002	0.008
1	Japan	206	122	40	34	9	1	0	≤0.002-0.03	≤0.002	0.008
1	All	726	475	122	95	29	5	0	≤0.002-0.03	≤0.002	0.008
14	US	14	2	9	3	0	0	0	≤0.002-0.008	0.004	0.008
14	Canada	3	1	1	0	0	1	0	≤0.002-0.03	NA	NA
14	N. America	17	3	10	3	0	1	0	≤0.002-0.03	0.004	0.008
14	Japan	3	1	2	0	0	0	0	≤0.002-0.004	NA	NA
14	All	20	4	12	3	0	1	0	≤0.002-0.03	0.004	0.008
15	US	38	12	19	5	2	0	0	≤0.002-0.015	0.004	0.008
15	Canada	3	1	2	0	0	0	0	≤0.002-0.004	NA	NA
15	N. America	41	13	21	5	2	0	0	≤0.002-0.015	0.004	0.008
15	Japan	11	3	4	3	1	0	0	≤0.002-0.015	0.004	0.008
15	All	52	16	25	8	3	0	0	≤0.002-0.015	0.004	0.008

NA = not applicable; no MIC data to determine range or number of isolates <10 so MIC₅₀ and MIC₉₀ were not calculated
Source: Study DSIN-7001-A6HP-39-11

Of the three principle dermatophyte species recovered in the clinical study, the MIC₉₀ values for *T. rubrum* (n = 798) and *T. mentagrophytes* (n = 73) were 0.008 mcg/mL and 0.015 mcg/mL, respectively (all visits). There were too few isolates of *E. floccosum* to calculate MIC₅₀ or MIC₉₀ values. The majority of isolates were collected at Visit 1 (n = 800, 91%). There were no significant changes noted in MIC values between isolates collected at Visit 1, and those collected at Visits 14 and 15.

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STUDY DPSI-IDP-108-P3-02

Study DPSI-IDP-108-P3-02 was performed in investigational centers in the U.S. (n=36) and Canada (n=8). Investigators randomized 580 patients to the active treatment arm and 201 patients to the vehicle arm. The Applicant reported no meaningful differences in baseline characteristics or demographics between the treatment arms. The analysis of the primary endpoint is summarized in Table 18. With regard to the Mycological Cure secondary endpoint, 53.4% of patients randomized to the IDP-108 arm and 16.9% of patients randomized to the vehicle arm had negative microscopy and dermatophyte cultures at the Week 52 Visit (p<0.001).

Table 18: Analysis of the primary efficacy endpoint at Week 52 (ITT subjects, DPSI-IDP-P3-02)

Number of subjects	<u>IDP-108</u> 580	<u>Vehicle</u> 201	
<u>Complete Cure at Week 52</u> ^a	<u>IDP-108</u>	<u>Vehicle</u>	<u>P-Value</u>
Success, n (%)	88 (15.2)	11 (5.5)	<u><0.001</u> ^b
Failure, n (%)	492 (84.8)	190 (94.5)	

^a A Complete Cure was defined as both 0% clinical involvement of the target toenail (i.e., the toenail was totally clear) in addition to a Mycologic Cure (i.e., a negative potassium hydroxide examination and a negative fungal culture of the target toenail sample).

^b P-value from a Cochran-Mantel-Haenszel test, stratified by analysis center.

Note: The last observation carried forward method was used to impute missing data prior to the analysis.

Source: Table 11-4 in the DPSI-IDP-108-P3-02 Clinical Study Report

Source: this submission, Module 2.7.3, page 46

A total of 906 fungal isolates were collected at the screening visit. Of these, the reference laboratory tested 789 isolates for susceptibility to efinaconazole and comparators (the remainder were either deemed too contaminated for further analysis or corresponded to study visits that were not relevant for the planned analysis). Tested dermatophyte species included *Trichophyton rubrum* (n = 751), *T. mentagrophytes* (n = 37), and *Epidermophyton floccosum* (n = 1) (Table 19). Approximately 88% of the tested isolates were from Visit 1. The reference laboratory reported “no meaningful differences in MIC between geographical locations and no increase in MIC was noted in specimens collected on Visits 14 or 15 as compared to Visit 1.” Study Report DSIN-7001-A6HP-39-11 includes a complete line list of all susceptibility test results performed on each isolate, as well as a complete record of quality control results.

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Table 19: Number of dermatophyte isolates tested for Study DPSI-IDP-108-P3-02

Isolate	Visit	US	Canada	North America
<i>Epidermophyton floccosum</i>	1	1	0	1
	14	0	0	0
	15	0	0	0
	Total	1	0	1
<i>Trichophyton mentagrophytes</i>	1	25	11	36
	14	0	0	0
	15	0	1	1
	Total	25	12	37
<i>Trichophyton rubrum</i>	1	555	106	661
	14	22	2	24
	15	59	7	66
	Total	636	115	751

North America = US + Canada
Source: Study DSIN-7001-A6HP-39-11

Summarized antifungal susceptibility data for the three principle fungal pathogens isolated in Study DPSI-IDP-108-P3-02 are summarized in Tables 20-22.

Table 20: Summary of in vitro susceptibility data for DPSI-IDP-108-P3-02 isolates of *Epidermophyton floccosum*

Visit	Country	No. Isolates	No. Isolates Inhibited at Concentration (µg/mL)						MIC (µg/mL)		
			≤0.002	0.004	0.008	0.015	0.03	0.06	Range	MIC ₅₀	MIC ₉₀
1	US	1	1	0	0	0	0	0	≤0.002	NA	NA
1	Canada	0	0	0	0	0	0	0	NA	NA	NA
1	N. America	1	1	0	0	0	0	0	≤0.002	NA	NA
14	US	0	0	0	0	0	0	0	NA	NA	NA
14	Canada	0	0	0	0	0	0	0	NA	NA	NA
14	N. America	0	0	0	0	0	0	0	NA	NA	NA
15	US	0	0	0	0	0	0	0	NA	NA	NA
15	Canada	0	0	0	0	0	0	0	NA	NA	NA
15	N. America	0	0	0	0	0	0	0	NA	NA	NA

NA = not applicable; no MIC data to determine range or number of isolates <10 so MIC₅₀ and MIC₉₀ were not calculated
Source: Study DSIN-7001-A6HP-39-11

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Table 21: Summary of in vitro susceptibility data for DPSI-IDP-108-P3-02 isolates of *Trichophyton mentagrophytes*

Visit	Country	No. Isolates	No. Isolates Inhibited at Concentration (µg/mL)						MIC (µg/mL)		
			≤0.002	0.004	0.008	0.015	0.03	0.06	Range	MIC ₅₀	MIC ₉₀
1	US	25	3	4	10	7	0	1	≤0.002-0.06	0.008	0.015
1	Canada	11	2	3	4	2	0		≤0.002-0.015	0.008	0.015
1	N. America	36	5	7	14	9	0	1	≤0.002-0.06	0.008	0.015
14	US	0	0	0	0	0	0	0	NA	NA	NA
14	Canada	0	0	0	0	0	0	0	NA	NA	NA
14	N. America	0	0	0	0	0	0	0	NA	NA	NA
15	US	0	0	0	0	0	0	0	NA	NA	NA
15	Canada	1	1	0	0	0	0	0	≤0.002	NA	NA
15	N. America	1	1	0	0	0	0	0	≤0.002	NA	NA

NA = not applicable; no MIC data to determine range or number of isolates <10 so MIC₅₀ and MIC₉₀ were not calculated

Source: Study DSIN-7001-A6HP-39-11

Table 22: Summary of in vitro susceptibility data for DPSI-IDP-108-P3-02 isolates of *Trichophyton rubrum*

Visit	Country	No. Isolates	No. Isolates Inhibited at Concentration (µg/mL)						MIC (µg/mL)		
			≤0.002	0.004	0.008	0.015	0.03	0.06	Range	MIC ₅₀	MIC ₉₀
1	US	555	304	170	71	10	0	0	≤0.002-0.015	≤0.002	0.008
1	Canada	106	54	36	15	1	0	0	≤0.002-0.015	≤0.002	0.008
1	N. America	661	358	206	86	11	0	0	≤0.002-0.015	≤0.002	0.008
14	US	22	8	11	3	0	0	0	≤0.002-0.008	0.004	0.008
14	Canada	2	1	1	0	0	0	0	≤0.002-0.004	NA	NA
14	N. America	24	9	12	3	0	0	0	≤0.002-0.008	0.004	0.008
15	US	59	25	23	11	0	0	0	≤0.002-0.015	0.004	0.008
15	Canada	7	2	1	3	1	0	0	≤0.002-0.015	NA	NA
15	N. America	66	27	24	14	1	0	0	≤0.002-0.015	0.004	0.008

NA = not applicable; no MIC data to determine range or number of isolates <10 so MIC₅₀ and MIC₉₀ were not calculated

Source: Study DSIN-7001-A6HP-39-11

Of the three principle dermatophyte species recovered in the clinical study, the MIC₉₀ values for *T. rubrum* (n = 798) and *T. mentagrophytes* (n = 73) were 0.008 mcg/mL and 0.015 mcg/mL, respectively (all visits). There were too few isolates of *E. floccosum* to calculate MIC₅₀ or MIC₉₀ values. The majority of isolates were collected at Visit 1 (88%). There were no significant changes noted in MIC values between isolates collected at Visit1, and those collected at Visits 14 and 15.

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COMBINED STUDIES

Results of the combined studies are summarized in Tables 23 and 24. With regard to the primary efficacy endpoint, 205 patients (16.6%) randomized to the efinaconazole arm demonstrated complete cure at the Week 52 visit, compared to 18 patients (4.3%) in the vehicle arm. In patients randomized to the efinaconazole arm, 54.2% had mycological cure at Week 52, compared to 16.9% in the vehicle arm.

Table 23: Analysis of the primary efficacy endpoint at Week 52 (ITT subjects, Phase 3 studies combined)

Number of Subjects	<u>IDP-108</u> 1236	<u>Vehicle</u> 415
<u>Complete Cure at Week 52</u>^a		
Success, n (%)	205 (16.6)	18 (4.3)
Failure, n (%)	1031 (83.4)	397 (95.7)

^a A Complete Cure was defined as both 0% clinical involvement of the target toenail (i.e., the toenail was totally clear) in addition to a Mycologic Cure (i.e., a negative potassium hydroxide examination and a negative fungal culture of the target toenail sample).

Note: The last observation carried forward method was used to impute missing data prior to the analysis.

Source: Table 14.2.2.2.1 in the Integrated Summary of Efficacy

Table 24: Analysis of the secondary endpoints at Week 52 based on Version 1 of the statistical analysis plan (ITT subjects, Phase 3 studies combined)

Number of subjects	<u>IDP-108</u> 1236	<u>Vehicle</u> 415
<u>Clinical Efficacy at Week 52</u>^a		
Success, n (%)	414 (33.5)	49 (11.8)
Failure, n (%)	822 (66.5)	366 (88.2)
<u>Mycologic Cure at Week 52</u>^b		
Success, n (%)	672 (54.4)	70 (16.9)
Failure, n (%)	564 (45.6)	345 (83.1)
<u>Unaffected new toenail growth at Week 52, (mm)</u>		
	<u>IDP-108</u>	<u>Vehicle</u>
	LSMEAN STDERR	LSMEAN STDERR
	4.3 5.7	1.1 4.6

Abbreviations: LSMEAN = least squares mean; STDERR = standard error

^a Clinical Efficacy was defined as an affected target toenail area of <10%.

^b A Mycologic Cure was defined as a negative potassium hydroxide examination and negative fungal culture of the target toenail specimen.

Note: The last observation carried forward method was used to impute missing data prior to the analysis.

Source: Table 14.2.2.3.1 in the Integrated Summary of Efficacy

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The Applicant reported collecting 1947 dermatophyte isolates during the course of the two studies. Of these, the central laboratory reported testing 1664 isolates for susceptibility to efinaconazole and comparators (the remainder were not shipped or rejected due to culture contamination or collection issues). For the combined clinical studies, the MIC₉₀ values for the two principle pathogens (those listed in the proposed indications for efinaconazole) were 0.015 mcg/mL and 0.008 mcg/mL for *T. rubrum* and *T. mentagrophytes*, respectively. The highest MIC noted in the clinical trial against any dermatophyte was 0.06 mcg/mL. All isolates tested with a narrow range of MICs. The predominant fungal species isolated in the two studies was *T. rubrum*. Isolation of *E. floccosum* was rare, and there were too few total isolates to determine MIC₉₀ or MIC₅₀ values (and too few to support inclusion in the proposed indications for efinaconazole). The Applicant did not provide an analysis of clinical or mycological efficacy based on correlation with MIC values. No resistance to efinaconazole was noted in the clinical studies.

The Applicant has included a table (Table 25) that summarizes the culture and susceptibility results from patients randomized to the efinaconazole arms of the 2 studies, who had a positive dermatophyte culture at baseline and at a late-stage visit (Week 48 and/or Week 52). All dermatophytes included in this analysis were *T. rubrum* (no isolates of either *T. mentagrophytes* or *E. floccosum* were isolated at late-stage visits, from patients randomized to receive efinaconazole). No genotyping was performed on the isolates described in this table, to confirm that late-stage isolates represented persistence (as opposed to reinfection). The MIC values of isolates obtained from each patient at the two (or three) time points were generally similar. Overall, no increase in MIC was observed during the course of the study for any of the three significant pathogens, indicating no increase in resistance in these fungi to efinaconazole during the course of the study.

Table 25: Listing of patients in Efinaconazole treatment arm with MIC data at Screening and at least Week 48 or Week 52 data

Patient ID	Isolate Genus	Isolate Species	Source (country)	MIC (µg/mL)		
				Screening	Week 48	Week 52
101-066	<i>Trichophyton</i>	<i>rubrum</i>	U.S.	0.008	NA	0.015
119-023	<i>Trichophyton</i>	<i>rubrum</i>	U.S.	≤0.002	0.008	NA
133-018	<i>Trichophyton</i>	<i>rubrum</i>	U.S.	≤0.002	0.004	0.004
184-012	<i>Trichophyton</i>	<i>rubrum</i>	Japan	0.008	NA	0.008
185-007	<i>Trichophyton</i>	<i>rubrum</i>	Japan	0.004	NA	0.008
218-016	<i>Trichophyton</i>	<i>rubrum</i>	U.S.	≤0.002	NA	0.004
223-043	<i>Trichophyton</i>	<i>rubrum</i>	U.S.	≤0.002	NA	≤0.002
232-030	<i>Trichophyton</i>	<i>rubrum</i>	U.S.	0.008	NA	0.004
233-055	<i>Trichophyton</i>	<i>rubrum</i>	U.S.	≤0.002	NA	0.004
244-114	<i>Trichophyton</i>	<i>rubrum</i>	U.S.	≤0.002	NA	≤0.002

NA = MIC data not available

No *T. mentagrophytes* isolates were recovered from the IDP-108 arms on Weeks 48 and 52

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Kerry Snow MS, MT(ASCP)

Clinical Microbiology Reviewer and Acting Clinical Microbiology Team Leader, DAIP

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/s/

KERRY SNOW
03/04/2013

Division of Anti-Infective and Ophthalmology Products
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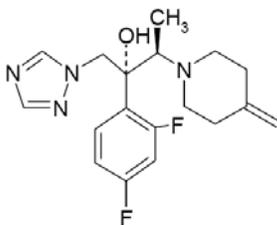
Date Received by CDER: 26 July 2012
Date Assigned: 17 August 2012
Date Mid-Cycle Review Completed: 5 December 2012
Reviewer: Kerry Snow

APPLICANT

Dow Pharmaceutical Sciences, Inc.
1330 Redwood Way
Petaluma, CA 94954-7121
Barry M. Calvarese, MS
Vice President
Regulatory and Clinical Affairs

DRUG PRODUCT NAME

Proprietary name: (b) (4)
Established name: Eflinaconazole Solution, 10%
Non-proprietary name: IDP-108 Topical Solution or KP-103 Topical Solution
Chemical name: C₁₈H₂₂F₂N₄O
Molecular formula: (2R,3R, 3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol
Molecular weight: 348.39
Chemical structure:



PROPOSED INDICATION

Treatment of (b) (4) onychomycosis of the toenails

**PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION
AND DURATION OF TREATMENT**

Form: liquid
Strength: (b) (4) 10% w/w of active ingredient, IDP-108
Route of Administration: topical
Duration: 48 weeks

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DISPENSED

Rx

RELATED DOCUMENTS

none

REMARKS

The Division of Dermatology and Dental Projects has requested a mid-cycle review of NDA 203567.

INTRODUCTION

(b) (4) (Efinaconazole Solution, 10%) is a novel triazole antifungal developed as a topical treatment for onychomycosis. Investigations have demonstrated a lower affinity of IDP-108 for keratin than currently marketed triazole antifungals. This property purportedly allows for greater mobility across the nail plate, and provides the principle rationale for development of the drug.

MECHANISM OF ACTION

The Applicant has submitted a study report (Study P090302) from a recent investigation of the mechanism of antifungal action of efinaconazole (KP-103). In this study, researchers measured the effect of efinaconazole on ergosterol synthesis in isolates of *T. mentagrophytes*, by comparing the concentration of [1,2-¹⁴C]-sodium acetate in sterol fractions. Results indicated that both efinaconazole and control (itraconazole) decreased the labeled sterols in ergosterol fractions (with concomitant increases in labeled sterol in the lanosterol fraction), in a concentration-dependent manner, when tested at sub-inhibitory concentrations against isolates of *T. mentagrophytes*. These results suggest a mechanism action in common with that proposed for azole antifungals.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The Applicant has submitted data from several studies designed to investigate the in vitro antifungal activity of efinaconazole. Three studies include data that is considered significant for this review. In these studies, tested fungi included recent isolates collected from clinical specimens in the U.S. (in addition to other geographic regions), and susceptibility testing was performed using methods approved by the Clinical and Laboratory Standards Institute (CLSI). In these three studies, efinaconazole compared favorably to comparators, and the MIC₉₀ value against isolates of *T. rubrum* (n = 199) and *T. mentagrophytes* (n = 205) were less than 0.03 mcg/mL and 0.10 mcg/mL, respectively. In a study performed to investigate the antifungal activity of efinaconazole against isolates

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of *C. albicans* (n= 105) the MIC₉₀ of eficonazole was 0.06 mcg/mL. The Applicant has also included a table summarizing the in vitro antifungal activity of efinaconazole against a variety of “other causative pathogens of onychomycosis in humans” (b) (4)

For the purposes of this submission, no single species was tested in numbers sufficient to permit meaningful microbiologic analysis. In addition, no rationale was provided to support the contention that any single species listed in the table is a significant pathogen typically associated with onychomycosis.

RESISTANCE STUDIES

The Applicant has submitted data from studies designed to investigate the potential for the development of resistance to efinaconazole in isolates of *T. rubrum* (Study P100304) and *T. mentagrophytes* (Study KP960608). Data from the serial passage study using isolates of *T. rubrum* indicate that after 12 passages, the development of resistance to efinaconazole was modest (2 of 6 isolates demonstrated an increase of 1 to 2 MIC doubling dilutions after 12 passages), which was superior to the comparator (itraconazole). In the similar study involving isolates of *T. mentagrophytes*, an MIC increase of one doubling dilution was noted after 10 serial passages, comparable to that observed in the comparator (clotrimazole). Preliminary review of the data collected in the clinical trials suggests no occurrence of resistance to efinaconazole in dermatophytes of interest (i.e. no MIC value greater than 0.06 mcg/mL).

SUSCEPTIBILITY TEST METHODS AND QUALITY CONTROL

The Applicant has included, in this submission, a study report that describes the development of quality control parameters to be used during antifungal susceptibility testing. This study is pending clinical microbiology review. No antifungal breakpoints have been proposed in this Application.

ANIMAL AND HUMAN STUDIES

ANIMAL MODELS OF INFECTION

The Applicant has submitted data from a study of the in vivo efficacy of efinaconazole in a guinea pig tinea unguium/pedis model. The clinical microbiology review of this study is pending.

HUMAN PHARMACOLOGIC STUDIES

The Applicant has submitted data from a study designed to investigate the efficacy of efinaconazole using a human toenail model of onychomycosis (Study KKN1001-02R). Preliminary review of the study supports the Applicant’s contention that the study

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demonstrates antifungal efficacy against isolates of *T. rubrum* in this model. Review of other PK/PD studies pertinent for clinical microbiological review is pending.

CLINICAL TRIALS

The complete clinical microbiology review of Studies DPSI-IDP-108-P3-01 and DPSI-IDP-108-P3-02 is pending. The preliminary review suggests that all microbiological testing was performed in a manner appropriate for meaningful analysis. Details of testing methods, as well as quality control results have been included in the study report. In the pooled studies, there were 1387 isolates of *T. rubrum* collected at the screening visit (726 in Study 01 and 661 in Study 02), 106 isolates of *T. mentagrophytes* collected at that visit (70 in Study 01 and 36 in Study 02), and 5 isolates of *E. floccosum* collected at the same visit (4 in Study 01 and 1 in Study 02). No isolate was tested during the course of the study with an MIC value greater than 0.06 mcg/mL.

PROPOSED LABEL

Based on the data reviewed to date, the clinical microbiology reviewer will recommend deletion of (b) (4) in the proposed product label. (b) (4)

CONCLUSIONS

The clinical microbiology review is proceeding on schedule. Information in the submission that is deemed pertinent for clinical microbiology review has been submitted in a clear and well-organized manner and appears sufficient for thorough analysis.

Kerry Snow
Clinical Microbiology Reviewer

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/s/

KERRY SNOW
12/08/2012

Clinical Microbiology: 45-Day Meeting Checklist NDA - Fileability
NDA 203567: Efinaconazole for the topical treatment of onychomycosis
Reviewer: Kerry Snow Date Review completed: 7 September 2012

On initial overview of the NDA application for RTF:

No.	Item	Yes	No	Comments
1	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	✓		
2	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin?	✓		
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?	✓		
4	On its face, has the applicant <u>submitted</u> <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains/ isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	✓		
5	Has the applicant <u>submitted</u> draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?			n/a
6	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓		
7	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	✓		

Clinical Microbiology: 45-Day Meeting Checklist NDA - Fileability
NDA 203567: Efinaconazole for the topical treatment of onychomycosis
Reviewer: Kerry Snow Date Review completed: 7 September 2012

8	Has the applicant <u>submitted</u> the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
9	Has the applicant <u>submitted</u> a clinical microbiology dataset in a format which intends to determine resistance development by correlating changes in the phenotype (such as <i>in vitro</i> susceptibility) and/or genotype (such as mutations) of the baseline relevant pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
10	Has the applicant used standardized methods or if non-standardized methods were used has the applicant included full details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	✓		
11	Is the clinical microbiology draft labeling consistent with 21 CFR Parts 201, 314, 601 and current Divisional policy.	✓		
12	FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? IF NO, GIVE REASONS BELOW.	✓		

Any Additional Clinical Microbiology Comments:

No additional comments.

Name of Reviewing Clinical Microbiologist

Kerry Snow

Acting Microbiology Team Leader

Peter Coderre, PhD

FIN 10 September 2012

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