# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203567Orig1s000

# MICROBIOLOGY / VIROLOGY REVIEW(S)

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.
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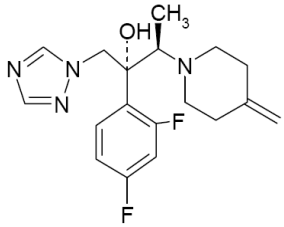
Petaluma, CA 94954-7121
Barry M. Calvarese, MS
Vice President
Regulatory and Clinical Affairs

## 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: $C_{18}H_{22}F_2N_4O$
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

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

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 14α-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 µg/mL or less against most [redacted] (b) (4) **(≥90%) of** isolates of the following microorganisms:

*Trichophyton mentagrophytes*

*Trichophyton rubrum*

[redacted] (b) (4)

(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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