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APPLICATION NUMBER:

203567Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	203567
Submission Date:	December 20, 2013
Brand Name:	JUBLIA
Generic Name:	Efinaconazole solution, 10%
Dosage Form:	Solution
Dosage Strength:	10%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
Division Director:	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Dermatology and Dental Products
Applicant:	Dow Pharmaceutical Sciences, Inc.
Relevant IND(s):	077,732
Submission Type:	Resubmission
Indication:	Topical treatment of onychomycosis in adults

Background and regulatory history: Efinaconazole is a new molecular entity (NME) and belongs to triazole antifungal drug class. The applicant is seeking an indication for once daily topical treatment of onychomycosis in adults with 10% solution formulation of efinaconazole. The original NDA was submitted on July 26, 2012 and this submission received a complete response due to Chemistry Manufacturing and Control (CMC) deficiencies on May 13, 2013 (see communication in DARRTS). The Clinical Pharmacology program submitted with the original application was found acceptable, provided the applicant adequately addressed the labeling comments (see Clinical Pharmacology review dated March 07, 2013, in DARRTS).

On December 20, 2013 the applicant re-submitted their NDA to address the CMC deficiencies. The applicant has changed the container closure system. No new Clinical Pharmacology or Clinical trials were conducted. In the opinion of the medical officer Dr. Gary Chiang, the steps adopted by the applicant to address the CMC issues do not warrant any new Clinical trials. Based on this assessment, additional Clinical Pharmacology trials will not to be needed to support an indication in adults.

Pediatric assessment: With the original NDA application, the applicant (b) (4) With this re-submission, the applicant has requested for a waiver in pediatric subjects from 0 - 11 years old and has provided the reason of low prevalence of onychomycosis in this age group. The applicant has requested a deferral to conduct pediatric assessment in subjects aged 12 to 17 years, post approval of this NDA in adults. Along with this submission, the applicant has submitted a synopsis of the proposed protocol (DPSI-IDP-108-P3-03), a vehicle controlled safety and efficacy trial of IDP-108 topical solution in pediatric subjects with mild to moderate onychomycosis of the toenails. The applicant has not proposed any pharmacokinetic (PK) assessment in this trial.

Reviewer comments: *To support an indication in pediatrics, the applicant will need to evaluate the PK of IDP-108 under maximal use conditions in the target pediatric population.*

This NDA was presented to the Pediatric Review Committee (PeRC) on April 30, 2014. PeRC recommended a waiver of <2 year of age group for reason that studies are impossible or highly impractical and a deferral for ≥2 years of age. This recommendation is similar to what PeRC has recommended previously for tavaborole (down to 6 years of age) and terbinafine (down to 2 years of age). The PeRC recommends opening up enrollment to younger ages to see whether subjects could be enrolled. In the tavaborole and terbinafine cases, DDDP had decided to move forward with waiver for <12 years and a decision along similar lines would likely be taken by DDDP for this NDA. PeRC agreed with Clinical Pharmacology recommendation to add PK assessment under maximal use conditions in a subset of pediatric subjects.

Summary of important Clinical Pharmacology findings: No new Clinical Pharmacology trials were conducted. The original submission contained 2 PK trials, Trial DPSI-IDP-108-P1-03 was a maximal use PK trial in adult subjects with severe onychomycosis and Trial DPSI-IDP-108-P1-02 was conducted in healthy adult subjects. The original NDA also contained information about drug metabolism and drug interaction assessment. These data were reviewed with the original application (for further information, see Clinical Pharmacology review dated March 07, 2013, in DARRTS).

Labeling recommendations: The Clinical Pharmacology detailed labeling recommendations were provided in the original NDA Clinical Pharmacology review (see review dated March 07, 2013 in DARRTS). Additional labeling edits that are being proposed in this review cycle are provided below.

With the original NDA application review, it was suggested to delete Section 7 – Drug Interactions. In this cycle, to be consistent with other recent labels, the review team decided to add this section and following is the addition shown as **bold and underlined text.**

7 Drug Interactions

No formal drug-drug interaction studies have been conducted with JUBLIA. In vitro studies have shown that JUBLIA, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

Reviewer comments: *Other than adding Section 7 to the label, no additional edits were made in Section 12.2 – Pharmacodynamics and Section 12.3 – Pharmacokinetics, in this review cycle.*

Recommendation: From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the applicant.

Post-marketing requirements: Pharmacokinetic assessment of IDP-108 under maximal use conditions in sufficient number of subjects aged 12 to 17 years with moderate to severe onychomycosis of the toenails.

Clinical Pharmacology briefing: An official briefing was not conducted for this NDA resubmission.

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/s/

CHINMAY SHUKLA
05/05/2014

DOANH C TRAN
05/05/2014

EDWARD D BASHAW
05/06/2014

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