CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203567Orig1s000

PHARMACOLOGY REVIEW(S)

Memorandum

To: NDA 203567
From: Linda S. Pellicore, Ph.D., Pharmacology/Toxicology Reviewer
Through: Barbara A. Hill, Ph.D., Pharmacology/Toxicology Supervisor
Re:

Submission date:	12/20/2013, 1/16/2014 and 2/4/2014
SDN:	21, 22 and 23
Submission type:	Resubmission Class 2
Drug:	JUBLIA (efinaconazole) Topical Solution, 10%
Drug class:	Azole antifungal
Indication:	Onychomycosis
Route:	Topical
Sponsor:	Dow Pharmaceutical Sciences

Background:

Efinaconazole is a new molecular entity (NME) and an azole antifungal drug. The applicant is seeking an indication for once daily topical treatment of onychomycosis in adults with JUBLIA (efinaconazole) topical solution, 10%. 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 nonclinical information submitted with the original application was found acceptable, provided the applicant adequately addressed the labeling comments (see Primary Nonclinical Review dated March 5, 2013, in DARRTS).

On December 20, 2013 the applicant re-submitted their NDA to address the CMC deficiencies. The applicant changed the container closure system. No new nonclinical information was submitted.

The sponsor resubmitted draft labeling information to the NDA on January 16, 2014. This nonclinical review pertains only to the sponsor's resubmitted draft labeling.

Review of proposed labeling:

Nonclinical detailed labeling recommendations were provided in the original NDA Primary Nonclinical Review (see review dated March 5, 2013 in DARRTS). In this cycle, the sponsor's proprietary name, JUBLIA, was found acceptable (see Proprietary Name Review dated March 26, 2014, in DARRTS). Other than adding the proprietary name to the sponsor's proposed label, no additional edits were made to the resubmitted draft labeling. Nonclinical labeling edits that are being proposed in this review cycle are provided below.

Conclusion:

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the JUBLIA (efinaconazole) Topical Solution 10% label reproduced below. The pharmacologic class designation for efinaconazole for the treatment onychomycosis is azole antifungal.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
JUBLIA (b) (4) azole antifungal (b) (4) indicated for the topical treatment of onychomycosis of the toenails due to *Trichophyton mentagrophytes* and *Trichophyton rubrum* (b) (4) (1)

8.1 Pregnancy
Pregnancy Category C

There are no adequate and well-controlled studies with JUBLIA topical solution in pregnant women- (b) (4). JUBLIA topical solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 2, 10 and 50 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-16) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal deaths, decreased number of live fetuses, and placental effects) was noted at 50 mg/kg/day [559 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No embryofetal toxicity was noted at 10 mg/kg/day (112 times the MRHD based on AUC comparisons). No malformations were observed at 50 mg/kg/day (559 times the MRHD based on AUC comparisons).

Subcutaneous doses of 1, 5, and 10 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rabbits. In the presence of maternal toxicity, there was no embryofetal toxicity or malformations at 10 mg/kg/day (154 times the MRHD based on AUC comparisons).

In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day efinaconazole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (17 times the MRHD based on AUC comparisons). No effects on postnatal development were noted at 25 mg/kg/day (89 times the MRHD based on AUC comparisons).

(b) (4)

(b) (4)

[redacted]

12.1 Mechanism of Action

JUBLIA topical solution is an azole antifungal [See *Clinical Pharmacology (12.4)*].

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4) A 2 year dermal carcinogenicity study in mice, was conducted with daily topical administration of 3%, 10% and 30% efinaconazole solution. Severe irritation was noted at the treatment site in all dose groups, which was attributed to the vehicle and confounded interpretation of skin effects by efinaconazole. The high dose group was terminated at week 34 due to severe skin reactions. No drug-related neoplasms were noted at doses up to 10% efinaconazole solution (248 times the MRHD based on AUC comparisons) (b) (4)

[redacted]

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration assay) and one in vivo genotoxicity test (mouse peripheral reticulocyte micronucleus assay) (b) (4)

[redacted]

(b) (4)

[redacted]

No effects on fertility were observed in male and female rats that were administered subcutaenous doses up to 25 mg/kg/day efinaconzole (279 times the MRHD based on AUC comparisions) prior to and during early pregnancy. Efinaconazole delayed the estrous cycle in females at 25 mg/kg/day but not at 5 mg/kg/day (56 times MRHD based on AUC comparisons).

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/s/

LINDA S PELLICORE
05/09/2014

BARBARA A HILL
05/09/2014

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