

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203567Orig1s000

OFFICE DIRECTOR MEMO

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 5, 2014
TO: NDA 203567 Jublia (efinaconazole) topical solution, 10%
 Dow Pharmaceutical Sciences, Inc.

FROM: Julie Beitz, MD
 Director, Office of Drug Evaluation III

SUBJECT: Approval Action

Jublia (efinaconazole) topical solution, 10% is an azole antifungal product indicated for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Jublia is applied to affected toenails once daily for 48 weeks using an integrated flow-through brush applicator. Efinaconazole is a new molecular entity.

This memorandum documents my concurrence with the Division of Dermatology and Dental Product's recommendation for approval of Jublia (efinaconazole) topical solution, 10%. Discussions regarding product labeling and postmarketing requirements and commitments have concluded and there are no inspectional issues that preclude approval.

REGULATORY HISTORY

NDA 203567 was submitted on July 25, 2012, and granted a standard review. While the clinical review identified no efficacy or safety issues that would preclude approval, product quality deficiencies were identified involving inadequate: 1) manufacturing process and controls for the filling/capping (b) (4) operation, 2) specifications for the drug product regarding leak detection, 3) integrity of the container closure system, and 4) stability data to assure the expiration dating period. A Complete Response letter was issued on May 13, 2013.¹

A post-action meeting was held with the applicant on July 17, 2013 to discuss the applicant's proposed control strategies to address the identified deficiencies. A complete response was submitted on December 20, 2013.

The application was not discussed before an FDA Advisory Committee as there were no novel or complex scientific or regulatory issues that required outside expertise. Efinaconazole is an antifungal product in the azole class, a class which includes several approved products.

PRODUCT QUALITY

Jublia (efinaconazole) topical solution, 10% is a clear colorless to pale yellow solution. Each gram contains 100 mg of efinaconazole. Jublia contains the following inactive ingredients: purified water, cyclomethicone, diisopropyl adipate, alcohol, C12-15 alkyl lactate, butylated

¹ For a detailed discussion of the first cycle review, see Dr. Victoria Kusiak's memorandum dated May 13, 2013.

hydroxytoluene, anhydrous citric acid, and disodium edetate. The alcohol content is approximately (b) (4) w/w in the product.

The drug product is manufactured by Kaken Pharmaceutical Co., Ltd. (Japan) by (b) (4)

(b) (4) In the complete response, the applicant proposed a new container closure system. Each bottle is fitted with an inside (b) (4) plug with a (b) (4) flow-through brush applicator and a (b) (4) cap.

The to-be-marketed container closure system was evaluated for chemical and physical stability, performance during in-use studies, photostability, presence of extractables and leachables, and comparability to the container closure system that was used in phase 3 trials.

Several manufacturing in-process controls have also been implemented, including periodic checks of fill weight, assessment of brush alignment and cap torque, and 100% visual inspection of packaging integrity.

The applicant's newly proposed container closure system and controls of the filling operation adequately address the Agency's previously identified deficiencies. The applicant's stability studies (24 months long-term and 6 months accelerated) support a 36 month expiration dating period, when stored under USP controlled room temperature conditions.

NONCLINICAL

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of *in vitro* (Ames assay and Chinese hamster lung cell chromosome aberration assay) and *in vivo* (mouse peripheral reticulocyte micronucleus assay) genotoxicity testing.

A 2-year 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. There was no treatment-related increase in neoplasms.

No effects on fertility were observed in male and female rats that were administered subcutaneous doses up to 25 mg/kg/day efinaconazole (279 times the maximum recommended human dose, MRHD) prior to and during early pregnancy.

PREGNANCY

Jublia will be classified as Pregnancy Category C and 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 rates. 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 MRHD²); congenital malformations were not observed at this dose. No embryofetal toxicity was noted at 10 mg/kg/day (112 times the MRHD).

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, no embryofetal toxicity or congenital malformations were noted at 10 mg/kg/day (154 times the MRHD).

In rats, subcutaneous doses of 1, 5 and 25 mg/kg/day efinaconazole were administered from the beginning of organogenesis through the end of lactation. In the presence of maternal toxicity, embryofetal toxicity was noted at 25 mg/kg/day (89 times the MRHD), including increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality. No effects on postnatal development were noted at this dose. No embryofetal toxicity was noted at 5 mg/kg/day (17 times the MRHD).

CLINICAL PHARMACOLOGY

Efinaconazole is an azole antifungal product that inhibits fungal ergosterol synthesis by inhibiting the enzyme lanosterol 14- α -demethylase. Inhibition of this enzyme's activity results in decreased amounts of ergosterol, a constituent of fungal cell membranes, and a corresponding accumulation of lanosterol. Efinaconazole has been shown to be active against isolates of *Trichophyton rubrum* and *Trichophyton mentagrophytes* both *in vitro* and in clinical infections.

A maximal use pharmacokinetic trial to assess systemic exposure resulting from use of efinaconazole was conducted in 18 subjects with severe onychomycosis. Efinaconazole was applied daily for 28 days to all ten toenails and to 0.5 cm of adjacent skin. Plasma concentrations of efinaconazole were near steady state by day 14.

Drug interactions. The potential for efinaconazole to inhibit CYP 450 enzymes 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2PE1, and 3A4 was evaluated *in vitro* using human liver microsomes. Efinaconazole did not inhibit the enzymatic activities of any of these CYP enzymes. The potential for efinaconazole to induce CYP 1A2 and CYP 3A4 was assessed *in vitro* using human primary hepatocytes; no induction of enzyme activity was observed.

EFFICACY

The efficacy of Jublia (efinaconazole) topical solution, 10% was demonstrated in two 52-week randomized, double-blind, vehicle-controlled trials of similar design. Subjects aged 18 years and older with onychomycosis involving 20-50% of the target toenail were randomized 2:1 to either 48 weeks of treatment with Jublia or vehicle solution. The primary efficacy endpoint, Complete Cure, defined as the proportion of subjects with 0% clinical involvement of the target toenail, negative KOH and negative fungal culture, was assessed at week 52.

² Multiples of human exposure were calculated based on comparisons between the maximal human AUC of 25.5 ng hr/mL in the maximal use clinical pharmacology trial and the AUCs for the NOAELs identified in the nonclinical studies.

Trial P3-01 enrolled 656 subjects on Jublia and 214 on vehicle solution. Trial P3-02 enrolled 580 subjects on Jublia and 201 on vehicle solution. Baseline demographics were similar in both trials. Complete Cure was significantly higher in the Jublia-treated groups compared to the vehicle-treated groups (17.8% vs. 3.3%, and 15.2% vs. 5.5%, in the two trials, respectively). Complete or Almost Complete Cure, defined in these trials as the proportion of subjects with less than or equal to 5% clinical involvement of the target toenail, negative KOH and negative fungal culture, was assessed at week 52. Treatment with Jublia was superior to vehicle in both trials (26.4% vs. 7.0%, and 23.4% vs. 7.5%, respectively).

Mycologic Cure, defined as the proportion of subjects with negative KOH and negative fungal culture, was assessed at week 52. Treatment with Jublia was superior to vehicle in both trials (55.2% vs. 16.8%, and 53.4% vs. 16.9%).

SAFETY

A total of 1227 subjects received Jublia in the two phase 3 trials submitted in the NDA. Of these, 1161 were exposed for at least 24 weeks and 780 were exposed for 48 weeks. In these trials, the most common adverse reactions were ingrown toenail and application site reactions (involving dermatitis, vesicles or pain). These occurred in 1-2% of Jublia-treated and in less than 1% of vehicle-treated subjects, respectively. Most adverse reactions were mild in severity.

PEDIATRICS

The **Pediatric Use** section of product labeling will state that the safety and effectiveness of Jublia in pediatric patients have not been established.

On April 30, 2014, the Pediatric Review Committee (PeRC) recommended a partial waiver request in pediatric patients ages 0 to 1 year 11 months for onychomycosis of the toenails because necessary studies are impossible or highly impracticable. The Division instead has recommended a partial waiver in pediatric patients ages 0 to 11 years 11 months, citing that culture positive onychomycosis due to *Trichophyton rubrum* and *Trichophyton mentagrophytes* is not prevalent in the pediatric population younger than 12 years of age. I concur with the Division's recommendation.

In addition, the PeRC recommended deferring submission of pediatric studies for ages 12 years to less than 17 years for this application because this product is ready for approval in adults and the pediatric studies have not been conducted.

The applicant will be required to conduct the following pediatric study post-approval:

- 1) A maximum use pharmacokinetic and safety study in pediatric subjects ages 12 years to less than 17 years with onychomycosis of the toenails.

TRADENAME REVIEW

On March 29, 2014, the applicant was notified by the Office of Medication Error Prevention and Risk Management that the proposed tradename "Jublia" was acceptable.

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

/s/

JULIE G BEITZ
06/05/2014