

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203567Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: May 23, 2014

Reviewer(s): Nyedra W. Booker, Pharm.D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK)

Team Leader: Reema Mehta, Pharm.D., M.P.H., DRISK

Division Director: Claudia Manzo, Pharm.D., DRISK

Drug Name(s): Jublia (efinaconazole) topical solution, 10%

Therapeutic Class: azole anti-fungal

Dosage and Route: Topical Solution (10%), applied to affected toenails

Indication(s): Onychomycosis of the toenail due to *Trichophyton mentagrophytes* or *Trichophyton rubrum*

Application Type/Number: NDA 203-567

Applicant/sponsor: Dow Pharmaceutical Sciences, Inc.

OSE RCM #: 2014-935

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## 1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the NDA 203-567 for Jublia (efinaconazole) topical solution (10%) to assess the need for a Risk Evaluation and Mitigation Strategy. A 505(b)(1) application for Jublia was received by the Division of Dermatology and Dental Products (DDDP) from Dow Pharmaceutical Sciences, Inc. on December 20, 2013,<sup>1</sup> to treat onychomycosis (b) (4). The Sponsor did not propose a REMS for Jublia.

### 1.1 PRODUCT BACKGROUND

Jublia (efinaconazole) is an azole antifungal developed for the topical treatment of onychomycosis. Pharmacologic activity is achieved through the inhibition of fungal lanosterol 14 $\alpha$ -demethylase involved in ergosterol biosynthesis, making Jublia first in a new pharmacologic class of topical azole antifungals.

Jublia is a topical solution developed to provide sufficient penetration to the diseased portion of the nail and nail bed without the need for debridement to deliver the active ingredient, in patients with onychomycosis of the toenails due to the dermatophytes *Trichophyton rubrum* or *Trichophyton mentagrophytes*.

Recommended dosage and administration of Jublia is as follows:

- Apply Jublia to affected toenails once daily for 48 weeks using the integrated brush applicator.
- When applying Jublia, ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate are completely covered.

Jublia is for topical use only and not for oral, ophthalmic, or intravaginal use.

### 1.2 DISEASE BACKGROUND

Onychomycosis<sup>2</sup> is a common fungal nail infection with a reported incidence of 2-13% in North America. While most cases are caused by dermatophytes and limited to toenail involvement, infection may also occur in the fingernails. Dermatophytic onychomycosis can be categorized as “distal subungual”, “proximal subungual”, and “white superficial.” Distal and proximal subungual onychomycosis most often result from *Trichophyton rubrum*, while white superficial onychomycosis is usually caused by *Trichophyton mentagrophytes*.<sup>3</sup> Older age, tinea pedis, and immunodeficiency are some of the risk factors for acquiring onychomycosis.

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<sup>1</sup> NDA 203-567 received a *Complete Response* on May 13, 2013, based on the following: 1) Inadequate manufacturing process and control information of the filling/capping (b) (4) operation, 2) Inadequate specification for the drug product, and 3) Inadequate integrity of the container closure system.

<sup>2</sup> (b) (4).

<sup>3</sup> (2013). Chapter 193. Onychomycosis. In Usatine R.P., Smith M.A., Chumley H.S., Mayeaux E.J., Jr. (Eds), *The Color Atlas of Family Medicine, 2e*. Retrieved March 13, 2014 from <http://accessmedicine.mhmedical.com/content.aspx?bookid=685&Sectionid=45361264>.

The clinical manifestations of onychomycosis include separation of the nail plate from the nail bed (onycholysis), subungual hyperkeratosis, and changes in the nail plate that make it thicker, brittle, and discolored. Symptoms include pain and other toenail discomfort when walking. Social embarrassment may also develop.

Treating onychomycosis can be challenging, as topical creams and lotions are often unable to sufficiently penetrate the nail plate, and oral agents may be associated with numerous potential drug interactions and severe systemic adverse effects.<sup>4</sup> Currently approved treatment options for onychomycosis include topical ciclopirox, oral griseofulvin, oral itraconazole, or oral terbinafine. Of the approved treatment options, none are marketed under a REMS program.

### **1.3 REGULATORY HISTORY**

July 26, 2012: Dow Pharmaceutical Sciences, Inc. submitted 505(b)(1) NDA 203-567 for Jublia topical solution, 10%

May 13, 2013: Dow Pharmaceutical Sciences, Inc. received a Complete Response based on Chemistry, Manufacturing, and Controls (CMC) finished product quality issues

April 16, 2013: Cross-Discipline Team Leader (CDTL) review concludes that Jublia would not require any risk management beyond product labeling and a REMS would not need to be considered for the application upon eventual approval

December 20, 2013: Dow Pharmaceutical Sciences, Inc. re-submitted 505(b)(1) NDA for Jublia topical solution, 10%

## **2 MATERIALS REVIEWED**

The following are a list of materials used to inform the review:

- Division of Anti-Infective Products (DAIP), Clinical Microbiology Review (K. Snow), dated May 17, 2014
- DDDP Clinical Review Resubmission (G. Chiang), dated May 16, 2014
- Draft Labeling for Jublia, dated May 15, 2014
- Dow Pharmaceutical Sciences, Inc. Clinical Overview for Jublia (NDA 203-567), dated July 26, 2013
- Dow Pharmaceutical Sciences, Inc. Summary of Clinical Safety for Jublia (NDA 203-567), dated July 26, 2013
- Dow Pharmaceutical Sciences, Inc. Summary of Clinical Efficacy for Jublia (NDA 203-567), dated July 26, 2013
- DDDP Cross-Discipline Team Leader Review (D. Kettl), dated April 16, 2013
- DDDP Clinical Review (G. Chiang), dated April 15, 2013

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<sup>4</sup> Botek, G. (2003). Fungal nail infection: Assessing the new treatment options. *Cleveland Clinic Journal of Medicine*, 110-118.

### 3 OVERVIEW OF CLINICAL PROGRAM

The clinical development program for Jublia included 9 clinical studies [four Phase 1 studies, one Phase 2 study<sup>5</sup>, two Phase 3 studies, and two additional studies providing supplemental safety data not conducted under the Investigational New Drug (IND) application]. The following pivotal Phase 3 studies formed the basis of safety and efficacy analyses:

<b>Studies P3-01 and P3-02</b>	
<b>Study Design</b>	Multi-center, randomized (3:1 ratio), double-blind, vehicle-controlled studies
<b>Inclusion Criteria</b>	Adults with a clinical diagnosis of mild to moderate distal lateral subungual onychomycosis affecting at least one great toenail. Disease severity defined as clinical involvement of 20%-50% of the area of the target great toenail, without dermatophytomas or lunula (matrix) involvement. The target toenail must have had an uninfected length $\geq 3$ mm (measured from the lunula), a thickness no greater than 3 mm, evidence of toenail growth, positive microscopic examination with KOH and positive fungal culture within 42 days prior to baseline visit.
<b>Treatment protocol</b>	Apply once daily at bedtime to all affected nails for 48-weeks.
<b>Primary endpoint</b>	“Complete Cure” defined as 0% involvement of the target great toenail, negative KOH examination and negative fungal culture of the target toenail, at Week 52 (four-week post-treatment follow-up visit).
<b>Treatment arms, sample size and study location</b>	P3-01; 74 investigational centers-US (34 centers), Japan (33 centers), and Canada (7 centers) <ul style="list-style-type: none"> <li>• Jublia (N=656); Vehicle (N=214)</li> </ul> P3-02; 44 investigational centers-US (36 centers) and Canada (8 centers) <ul style="list-style-type: none"> <li>• Jublia (N=580); Vehicle (N=201)</li> </ul>

#### 3.1 EFFICACY

The primary efficacy endpoint (percentage of patients in each treatment group achieving a “Complete Cure” at Week 52) was met in both pivotal studies. Jublia solution (10%) was statistically and clinically more effective than the vehicle in providing a “Complete Cure” at Week 52, with cure rates of 17.8% in subjects treated with Jublia in P3-01 and 15.2% in Jublia-treated subjects in P3-02. Complete Cure for vehicle-treated subjects was 3.3% and 5.5% for P3-01 and P3-02 respectively.

Efficacy of Jublia versus vehicle was also demonstrated in both trials, for all three secondary endpoints ( $p < 0.001$ ) as presented in Table 1.

Table 1: Secondary Efficacy Endpoints Analysis

<b>Trial</b>	<b>Secondary Endpoints<sup>6</sup></b>	<b>Jublia 10%</b>	<b>Vehicle</b>
<b>P3-01</b>	<b>Complete or almost complete cure</b>	173/656 (26%)	17/214 (7%)
	<b>Mycologic cure</b>	362/656 (55%)	36/214 (17%)
	<b>Unaffected new nail growth in mm</b> (change from baseline in healthy target nail measurement)	5.0 (0.2)	1.6 (0.4)
<b>P3-02</b>	<b>Complete or almost complete cure</b>	136/580 (23%)	15/201 (7%)

<sup>5</sup> The Phase 2 study was a dose-ranging study conducted with the original efinaconazole formulation, NOT the to-be-marketed Jublia formulation.

<sup>6</sup> The secondary endpoint “Complete or almost complete” cure was defined by  $\leq 5\%$  affected toenail and mycological cure (negative KOH and culture).

	<b>Mycologic cure</b>	310/580 (53%)	34/201 (17%)
	<b>Unaffected new nail growth in mm</b> (change from baseline in healthy target nail measurement)	3.8 (0.2)	0.9 (0.4)

**DDDP Clinical Reviewer Comment:** *The secondary endpoints were supportive to the primary efficacy of this drug product. In the opinion of this reviewer, the supportive secondary measures are not clinically relevant* (b) (4)

### 3.2 SAFETY

The Phase 3 safety population consisted of 1655 subjects randomized to receive topical treatment with Jublia (1239 subjects) or vehicle (416 subjects) once daily for 48 weeks. A total of 1227 subjects applied the active study drug at least once, and of the 1655 enrolled subjects, 86.8% completed the 48-week treatment period and 85.8% completed the entire 52-week study.

The safety evaluation consisted of the following: reported adverse events, laboratory tests, and electrocardiogram (ECG) data.

The most common treatment-related adverse events (AEs) occurring in >1% of subjects receiving Jublia (and at greater frequency than observed with vehicle) included application site dermatitis and application site vesicles<sup>7</sup>. Systemic exposure to Jublia was low, and no systemic toxicities were identified. There were also no clinically meaningful trends observed related to laboratory values and ECG findings.

There were 65 serious adverse events (SAEs) reported during Phase 3 studies; none were deemed treatment-related.

**DDDP Clinical Reviewer Comment:** *The SAEs experienced by the subjects in the combined Phase 3 clinical trials are unlikely related to study drug. None are recommended for labeling by this reviewer.*

A total of 33 subjects (all but one receiving Jublia) discontinued the study due to an adverse event. Most of these events were associated with application site reactions. Two deaths were reported during Phase 3 studies; both deaths were determined to be unlikely related to Jublia treatment.

**DDDP Clinical Reviewer Comment:** *The majority of AEs related to investigational drug product are application site reactions, some of which caused discontinuation of study drug or study. The two deaths involved in the Phase 3 clinical trials are unlikely related to investigational drug. The first subject died of reported suicide. It is unlikely that a topical antifungal with low systemic absorption would cause the psychological effects enabling a suicide attempt. In the second case of squamous cell carcinoma, the advance stage of the disease and metastasis tells this reviewer that the patient likely had undiagnosed lung cancer prior to the start of the onychomycosis trial. It is unlikely that this drug product increased the likelihood of metastasis or caused the squamous cell lung cancer.*

<sup>7</sup> Application site vesicle is a small bubble that can form within the cell at the application site of a drug.

## 4 DISCUSSION

Jublia has the ability to penetrate the nail plate to the bed of infected nails, with low systemic absorption following topical application. If approved, Jublia would represent the first in a new class of topical azole antifungals. According to the DDDP clinical reviewer, Jublia may be a reasonable option for patients with onychomycosis who do not wish to undergo more comprehensive topical treatment required<sup>8</sup> with Penlac<sup>®</sup>, currently the only approved topical product in the U.S. to treat toenail onychomycosis. Penlac<sup>®</sup> Nail Lacquer (ciclopirox) Topical Solution, 8%, does not have REMS program requirements.

Jublia has demonstrated clinical benefit in the treatment of onychomycosis due to the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Treatment related AEs consisted of application site reactions and local skin reactions, which is expected for topical products. Systemic exposure with Jublia is low. The safety profile of Jublia is similar to that of other topical azole antifungal medications. There are no serious risks identified at this time to warrant a REMS. The professional labeling for Jublia will include ingrown toenails, application site dermatitis, application site vesicles, and application site pain as ADVERSE REACTIONS.

## 5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Jublia (efinaconazole) topical solution (10%). Jublia has demonstrated efficacy in the treatment of onychomycosis. There were no serious risks of concern identified during the review of the application that required mitigation beyond labeling. Thus, the benefit-risk profile for Jublia is acceptable and the risks, like with other topical azole antifungals, can be mitigated through professional labeling.

Should DDDP have any concerns or questions, or feel that a REMS may be warranted for this product, please send a consult to DRISK.

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<sup>8</sup> Penlac<sup>®</sup> requires up to 48 weeks of daily applications. Professional removal of the unattached, infected nail, as frequently as monthly, is considered the full treatment needed to achieve a clear or almost clear nail (defined as 10% or less residual nail involvement).

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05/23/2014

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