CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203567Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Stanka Kukich, MD
Subject	Deputy Director Summary Review
NDA	203567
Applicant Name	Dow Pharmaceutical Sciences/Valeant Pharmaceuticals North America LLC
Date of Submission	December 20, 2013
PDUFA Goal Date	June 20, 2014
Proprietary Name / Established (USAN) Name	JUBLIA/Efinaconazole
Dosage Forms / Strength	Topical solution, 10%
Proposed Indication(s)	Treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Gary Chiang, MD
Statistical Review	Kathleen Fritsch, PhD
Pharmacology Toxicology Review	Linda Pellicore, PhD
CMC Review/OBP Review	Bogdan Kurtyka, PhD
Microbiology Review	Kerry Snow, MS
Clinical Pharmacology Review	Chinmay Shukla, PhD
CDTL Review	David Kettl, MD
OSE/DMEPA	Carlos Mena-Grillasca, RPh

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This is a resubmission in response to the Agency's original action of May13, 2013 and provides for the use of JUBLIA (efinaconazole) topical solution, 10% for the treatment of onychomycosis of the toenails due to *Trichophyton mentagrophytes or Trichophyton rubrum*.

Efinaconazole is a new molecular entity, an azole antifungal agent, for the topical treatment of onychomycosis (tinea unguium) of the toenails. It is applied to toenails, the nail folds, nail bed, hyponychium, and undersurface of the nail plate once daily for 48 weeks using a flow-through brush applicator.

IND for IDP-108 (efinaconazole) was submitted by Dow Pharmaceutical Sciences on June 14, 2007 and NDA on July 26, 2012. Initially, this application received a Complete Response action on May 13, 2013 because of the lack of sufficient chemistry, manufacturing, and controls (CMC) information. The CMC deficiencies included, but were not limited to, brush-cap assembly, integrity of the container /closure system, inadequate specification for the drug product, and inadequate stability data to assure the expiration period.

The applicant has replaced the original container with a similar container closure system that does not leak under accelerated or long-term conditions when stored in either horizontal or vertical position. The formulation, manufacturing process, specifications and analytical methods for the drug substance, excipients, and the final product are the same as described in the original NDA. The container closure and the location of the finished product manufacturing have been changed. Additionally, a more rigorous in-process control for the packaging operation has been added.

JUBLIA has been approved in Canada, however, has not been marketed at the time of resubmission of the NDA.

This review will discuss issues under sections 3, 10, 11, 12, and 13 that are related to information provided in resubmission of this NDA. For the complete review of other sections please refer to the Summary Review for Regulator Action, April 24, 2013.

2. Background

Onychomycosis is a chronic fungal infection of nail plate due to dermatophytes, nondermatophytes and yeasts. Common dermatophytes causing onychomycosis (tinea unguium) are *Trichophyton mentagrophytes, Trichophyton rubrum,* and *Epidermophyton floccosum.* The prevalence rate of onychomycosis is 2% to 14%. It is more prevalent in adults

and is less common in children (prevalence rate 0.2% to 2.6%). Often patients with a chronic tinea pedis and tinea manuum also have infection of the nails. The infection usually starts at the distal edge of the nail, presented as an opaque white, then yellow to brown patch at the side and distal tip of the nail. Some of the poor prognostic factors include, but are not limited to, area of nail involvement >50%, presence of dermatophytoma, matrix involvement, and immunosuppression. The criteria for diagnosis of onychomycosis include clinical evaluation, potassium hydroxide (KOH) microscopic evaluation, and fungal culture.

Efinaconazole is an azole antifungal agent that inhibits fungal lanosterol 14-α demethylase involved in ergosterol biosynthesis. Loss of ergosterol in the fungi cell wall may be responsible for the fungistatic and fungicidal activity. Efinaconazole has been shown to be active against *Trichophyton mentagrophytes and Trichophyton rubrum*, both, invitro and in the clinical setting.

Regulatory issues regarding the development program for this product were discussed with the applicant at the End-of-Phase 2 meeting on August 4, 2009 and Pre-NDA meeting on April 11, 2012. The Type A meeting was held on July 17, 2013 to discuss the Complete Response Letter. In addition, there were a number of interactions with the applicant during the development of efinaconazole under the IND and during the review process of the submitted NDA. These interactions included teleconferences, correspondences, and advice letters.

3. CMC/Device

Each gram of JUBLIA contains 100 mg of efinaconazole in a clear, colorless to pale yellow solution. It is manufactured by (b) (4) . The drug substance is insoluble in water. The alcohol content is approximately (b) (4) w/w in the product.

In the Complete Response letter, the following product quality issues were identified: a) inadequate manufacturing process and control information of the filling/capping (b) (4) operation, b) inadequate specification for the drug product, c) inadequate integrity of the container closure system, and d) inadequate stability data to assure the expiration dating period.

In this submission, the applicant proposed a new container closure system of similar design that includes 10 mL HDPE bottle with a flow-through brush applicator. The container closure, packaging operations, and the manufacturing facility are new. Manufacturing process included all necessary controls to assure drug product quality, 24 months stability data on three representative batches in the new container were submitted, and information on Kaken's cGMP manufacturing facility was also included.

Drug product specification and analytical methods for the drug substance, excipients, and the formulation were not changed from the original submission.

Based on Chemistry Manufacturing and Controls assessment, 1) the DMF has been reviewed and found adequate to support manufacturing process for efinaconazole, 2) the drug product specification and analytical methods were found acceptable for assuring the identity, strength, purity, and quality of drug product, 3) the new container closure system and control of filling operation were adequately addressed previous concerns, 4) results of 24-month stability studies supported 36-month expiration period, 5) the cGMP compliance of facilities (including the new drug product manufacturer proposed in the resubmission) has been deemed acceptable by the Office of Compliance.

The new product packing configuration appears sufficiently similar regarding application technique and amount of product delivered to the one used in clinical trials. Therefore, the new container closure presentation does not change safety and efficacy conclusion reached in the clinical trials where previous packaging was used.

Efinaconazole formulation is flammable due to high alcohol content.

4. Nonclinical Pharmacology/Toxicology

Refer to the previous Summary Review for Regulatory Action of April 24, 2013

5. Clinical Pharmacology/Biopharmaceutics

Refer to the previous Summary Review for Regulatory Action of April 24, 2013

6. Clinical Microbiology

Refer to the previous Summary Review for Regulatory Action of April 24, 2013

7. Clinical/Statistical-Efficacy

No additional clinical trials were conducted since Complete Response Action was issued for this application.

Refer to the previous Summary Review for Regulatory Action of April 24, 2013

8. Safety

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