CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205175Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	October 21st, 2013
From	Susan J. Walker, MD, FAAD
Subject	Division Director Summary Review
NDA #	205175
Applicant Name	AmDerma Pharmaceuticals, LLC
Date of Submission	December 26th, 2012
PDUFA Goal Date	October 25th, 2013
Proprietary Name / Established (USAN) Name	Ecoza/ Econazole nitrate
Dosage Forms / Strength	Foam, 1%
Proposed Indication(s)	1. Interdigital tinea pedis
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Amy Woitach, MD
CDTL Review	David Kettl. MD
Statistical Review	Kathy Fritsch, PhD
Pharmacology Toxicology Review	Jerry Wang, PhD
ONDQA/CMC Review ONDQA Biopharm	Nina Ni, PhD Kelly Kitchens, PhD
Clinical Microbiology Review	Shukal Bala, PhD
Clinical Pharmacology Review	Chinmay Shukla, PhD
OMP	Karen Dowdy,RN,BSN Kemi Asante, PharmD
OSE	Carlos Mena-Grillasca

OND=Office of New Drugs
CDTL=Cross-DisciplineTeam Leader
ONDQA=Office of New Drug Quality and Assessment
CMC =Chemistry, manufacturing and controls
OMP= Office of Medical Policy
OSE= Office of Surveillance and Epidemiology

Signatory Authority Review

1. Introduction

This application proposes the use of Econazole nitrate foam 1% [redacted] (b) (4) The review team is in agreement in recommending approval of the product for the treatment of interdigital tinea pedis and there are no outstanding or controversial issues remaining for this application. I concur with the recommendations of the review team. This summary review will focus upon the primary review conclusions and will contain excerpts from the individual reviews and the team leader summary review.

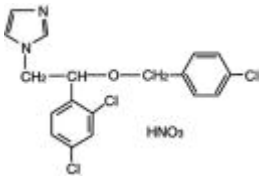
2. Background

Tinea pedis is a dermatophytic infection of the feet characterized by erythema and chronic desquamation between the toes (interdigital type) or with widespread erythema, hyperkeratosis, and scaling on the sole and heel of the foot (moccasin or plantar type). Diagnosis of tinea pedis is usually by physical examination, in combination with laboratory evidence of the fungal organisms by direct microscopic examination with potassium hydroxide (KOH) followed by culture for dermatophytes.

3. CMC/Device

Ecoza (econazole nitrate) topical foam, 1% contains the azole antifungal agent, econazole nitrate in an oil-in-water emulsion base consisting of the following inactive ingredients: dimethicone, glycerin, polysorbate 20, povidone, propylene glycol, stearic acid, trolamine, purified water and butane as a propellant. Each gram of Ecoza topical foam, 1% contains 10 mg of econazole nitrate, USP, in a white to off-white foam. Ecoza topical foam, 1% is alcohol (ethanol)-free and for topical use only.

Chemically, econazole nitrate is 1-[2-{(4-chloro-phenyl)methoxy}-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole mononitrate. Econazole nitrate has the molecular formula $C_{18}H_{15}Cl_3N_2O.HNO_3$ and a molecular weight of 444.70. Its molecular structure is as follows:



I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review fully evaluated the systemic bioavailability of the product and the potential for drug interactions. I concur with the recommendation for a post- marketing evaluation of potential drug-drug interactions as delineated in the post-marketing requirement for this product.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

In two multi-center, randomized, double-blind, vehicle-controlled clinical trials a total of 505 subjects with interdigital tinea pedis were randomized 1:1 to Ecoza topical foam or vehicle;

subjects applied the assigned medication once daily for 4 weeks. The severity of erythema, scaling, fissuring, maceration, vesiculation, and pruritus were graded using a 4-point scale (none, mild, moderate, severe). Subjects had KOH examination and fungal cultures taken to confirm eligibility. A total of 339 subjects with positive fungal cultures were evaluated for efficacy. Efficacy was evaluated on Day 43, 2 weeks post-treatment with treatment success being defined as complete cure (negative KOH and fungal culture and no evidence of clinical disease). The study population ranged in age from 12 to 71 years with 5 subjects less than 18 years of age at baseline. The subjects were 71% male and 52% Caucasian. Table 1 presents the efficacy results for each trial.

Table 1: Efficacy Results at Two Weeks Post-treatment (Day 43)
Complete Cure, Effective Treatment and Mycological Cure

	Trial 1		Trial 2	
	Ecoza topical foam, 1% N = 82 n(%)	**Foam Vehicle N = 83 n(%)**	**Ecoza topical foam, 1% N = 91 n(%)**	**Foam Vehicle N = 83 n(%)**
Complete cure[a]	19 (23.2%)	2 (2.4%)	23 (25.3%)	4 (4.8%)
Effective treatment[b]	40 (48.8%)	9 (10.8%)	44 (48.4%)	9 (10.8%)
Mycological cure[c]	56 (68.3%)	13 (15.7%)	61 (67.0%)	15 (18.1%)

[a]Mycological cure and an absence of clinical signs and symptoms (erythema, scaling, fissuring, maceration, vesiculation, or pruritus).
[b]Mycological cure and no or mild erythema and/or scaling with all other signs and symptoms absent.
[c]Negative KOH and fungal culture.

8. Safety

No safety issues were identified in the Phase 1 or Phase 2 studies. No safety issues have been identified that would preclude approval for the treatment of interdigital tinea pedis in patients 12 years of age and older.

In two double-blind, vehicle-controlled clinical trials, 495 subjects were exposed to Ecoza topical foam or vehicle (246 subjects were exposed to Ecoza topical foam, 1% and 249 were exposed to vehicle). Subjects with interdigital tinea pedis applied foam or vehicle once daily for approximately 28 days. During clinical trials with Ecoza topical foam, the most common adverse reactions were application site reactions which occurred in less than 1% of subjects in both the Ecoza and vehicle arms.

The data base for Econazole Nitrate Foam, 1% also includes 698 subjects who were randomized/ enrolled in open-label studies. Most of these subjects received at least 1 treatment dose with the majority of subjects completing treatment. Similar proportions of econazole foam and vehicle foam subjects experienced adverse events during the phase 3 studies (13% vs. 12% respectively in Study 302 and 10% vs. 10% in Study303). 614 subjects

reported 85 AEs. Few adverse events occurred in more than one subject per arm, and those that did (headache and nasopharyngitis) generally occurred in similar rates in all treatment arms. No deaths, pregnancies or treatment-related SAEs were reported in subjects treated with Econazole Nitrate Foam, 1%.

There have been cases of drug interactions between topical econazole nitrate cream and anticoagulant therapy with coumarins (warfarin and acenocoumarol) reported in the FDA Adverse Event Reporting System (FAERS) and medical literature. The Agency Division of Pharmacovigilance (DPV) evaluated the case reports in association with econazole use and recommended including language in all econazole labels regarding drug-drug interaction with warfarin, resulting in an increased anticoagulant effect of coumarins in association with topical econazole use. While there were no cases identified in the development program for this econazole foam formulation, the review team recommends including this drug interaction in labeling for this product. I concur with the conclusion of the clinical reviewer, Dr Woitach, that this be addressed as a post-marketing requirement. The sponsor has agreed to conduct in-vitro assessments to evaluate the inhibition and induction potential of Econazole nitrate. While the evidence of drug-drug interactions is not robust, and the adverse event reports were within the context of off label/excessive use of a similar marketed product, it would be prudent to continue investigation of this potential adverse event.

The assessments will evaluate the in-vitro potential of econazole to inhibit enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 or induce CYP1A2, CYP2B6 and CYP3A. The results will be compared with the systemic econazole concentration expected from clinical use to determine whether there is a potential for in-vivo drug interaction. Additional in-vivo drug interaction trials may be needed based on in-vitro results. Inhibition potential may lead to increased exposure to interacting drug and potentially increased adverse reactions. Induction potential may lead to decrease exposure to interacting drug and potentially lead to decreased efficacy.

9. Advisory Committee Meeting

No advisory committee meeting was conducted for this application. Econazole has a thirty year marketing history and there were no necessary salient discussions.

10. Pediatrics

The Sponsor conducted a pediatric PK trial (Trial 0792951-109) under maximal use conditions in subjects 12 to 17 years of age with interdigital tinea pedis. Labeling for pediatrics is based on this study as well as the results from the two phase 3 trials. For subjects 11 years of age and younger, the applicant requested and was granted a partial waiver of pediatric studies, as studies are impossible or highly impracticable in this indication.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

- There are no unresolved labeling issues.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - The product will be approved.
- Risk Benefit Assessment: All disciplines recommend approval and in my opinion the benefits of this product outweigh the risks.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies: None
- Recommendation for other Postmarketing Requirements and Commitments:

2087-1 Conduct in-vitro assessments to evaluate the following:

1. Inhibition potential of econazole nitrate for enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4.

2. Induction potential of econazole nitrate for enzymes CYP1A2, 2B6 and 3A.

Further in-vivo assessment to address drug interaction potential may be needed based on the results of the in-vitro assessment.

The timetable will be according to the following schedule:

Final Protocol Submission:	11/13
Study Initiation:	05/14
Final Report Submission:	10/14

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/s/

SUSAN J WALKER
10/24/2013