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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 6, 2013
From	David Kettl, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 204175 Related IND: 77,523
Applicant	AmDerma Pharmaceuticals, LLC
Date of Submission	December 26, 2012
PDUFA Goal Date	October 25, 2013
Proprietary Name / Established (USAN) names	Ecoza (econazole) topical foam 1%
Dosage forms / Strength	Topical foam
Proposed Indication(s)	Interdigital tinea pedis
Recommended:	*Approval*

1. Introduction

The applicant, AmDerma Pharmaceuticals, LLC, submitted this 505 (b)(2) application for econazole nitrate foam, 1%, for the proposed indication of interdigital tinea pedis (b) (4)

The review team is in full concurrence that an approval recommendation is warranted for this product applied topically once-daily for 4 weeks in treatment of interdigital tinea pedis, pending successful completion of labeling negotiations.

The clinical review, by Dr. Amy Woitach, identified no significant safety or efficacy issues to impact the conclusion that sufficient evidence is provided in this application to reasonably demonstrate that the benefit of the drug product outweighs the risks when used according to the prescribing information. Most notably, adverse reactions were generally mild and were confined to application site reactions.

This product was submitted as a 505(b)(2) application and the applicant proposes to rely upon the Agency's finding of safety for Spectazole Cream (econazole nitrate), 1% to support this NDA. Because Spectazole Cream was discontinued from marketing (not for reasons of safety or effectiveness), the generic drug product Econazole Nitrate Cream, 1%, manufactured by Fougera, was used as the comparator in the clinical bridging study.

This CDTL review concurs with the team's recommendation of approving econazole topical foam 1% for the **topical treatment of interdigital tinea pedis caused by *T. rubrum, E. floccosum or T. mentagrophytes*,** and concurs with the post marketing requirements discussed below. There are no outstanding issues from any review discipline, and draft labeling and recommended post marketing requirements have been provided to the applicant.

2. Background

Proposed Indication:
Tinea pedis is a fungal infection of the foot and is usually caused by dermatophytes, aerobic fungi that produce keratinase, an enzyme that breaks down in the stratum corneum of the skin. The vast majority of tinea pedis cases are caused by *T. rubrum, E. floccosum* or *T. mentagrophytes*.

The clinical manifestations of tinea pedis usually present as a pruritic, erythematous, inflamed area of the foot most often seen between the toes (interdigital type) or a more severe, prolonged form that may involve the entire bottom and lateral aspects of the foot (moccasin type) or sometimes located on the sole (vesicular 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.

The applicant seeks an indication for interdigital tinea pedis. Moccasin type tinea pedis was not evaluated in the development program.

Proposed Drug Product: Econazole
Econazole nitrate is an azole antifungal and has broad-spectrum antifungal activities, and has been marketed in the United States for more than thirty years, initially as a cream formulation approved in 1982. Spectazole (econazole nitrate) Cream 1%, (NDA 18751) was approved on 12/23/1982, but was recently discontinued for business reasons by Ortho Janssen. The product used in the clinical trials was approved as ANDA 76075, Econazole nitrate cream 1%, on 11/26/2002, marketed by Fougera.

The currently approved econazole products have indications beyond interdigital tinea pedis. Econazole Nitrate Cream, 1% is approved as a once daily application for the topical treatment of tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Microsporum canis, Microsporum audouini, Microsporum gypseum and Epidermophyton floccosum*, and for the treatment of cutaneous candidiasis and the treatment of tinea versicolor.

The IND for econazole foam was opened in 2008 with the protocol for the Phase 2 study (Study 207). Four meetings were held between the sponsor and the Agency during the IND development: Pre-IND (2007), End-of-Phase 2 (2009), Post-SPA (2010), and Pre-NDA (2012). Both Phase 3 studies (Studies 302 and 303) were evaluated under Special Protocol Assessments. Both protocols received Agreement letters and general agreement was reached on the study design, endpoints, and analysis, with one exception. The sponsor originally proposed designing Study 303 as a three-arm study without a vehicle cream arm. Based on the Agency's recommendation, the sponsor modified the design to include a vehicle cream arm in Study 303 so that the design aligned with the Agency's recommendations.

The clinical program for this application consists of four Phase 1 dermal safety trials, two Phase 2 trials which include an adult pharmacokinetic (PK) trial to support a bridge between the econazole foam and cream formulations and a pediatric PK trial in subjects 12 to 17 years of age under maximal use conditions and two Phase 3 trials.

3. CMC/Device

No critical issues were identified during the review cycle by the CMC reviewer, Dr. Nina Ni. Review issues related to solubility of the drug product (b) (4) were successfully resolved following informational requests with the applicant.

The proposed drug product specification which includes description, identity, pH, pressure, delivered amount, dispensing rate, appearance (b) (4) by both visual and microscopic observation, assay, (b) (4) packaging/product interactions, (b) (4) and microbiological testing, are supported by batch data and were deemed acceptable.

The proposed drug product is a white to off-white foam packaged in pressurized (b) (4) cans. The filling weights are 70 g and 10 g for the physician sample.

The primary container/closure system for the drug product consists of a metal can, a valve, an actuator, and an over cap. All the components except for steel spring, comply with the pertinent 21CFR regulations for direct food contact. There is no safety concern for the container/closure system.

There are no novel excipients. All the inactive ingredients are below approved levels listed in the FDA's database of inactive ingredients in approved drug products.

Microbial control information for the drug substance, excipients, and drug product was reviewed and found adequate by the Agency microbiologist, Dr. Erika Pfeiler.

An IVRT study was conducted to bridge a manufacturing site change (b) (4) as well as minor process changes. The in vitro release testing (IVRT) method and its validation was reviewed and found adequate by Dr. Kelly Kitchens from ONDQA.

The Office of Compliance has concluded an overall "Acceptable" recommendation for the facilities involved in this application.

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. There are no outstanding issues from a chemistry perspective beyond completion of labeling negotiations.

4. Nonclinical Pharmacology/Toxicology

The applicant proposes a 505 (b)(2) pathway for the application, and includes an econazole cream arm in a phase 3 clinical trial to help establish a clinical bridge to the safety and efficacy findings for econazole nitrate cream. Most of the required nonclinical elements are satisfied by reference to the existing information from the cream formulation.

In addition to relying upon the Agency's finding of safety for the listed drug, the applicant conducted a dermal irritation study in rabbits, a dermal sensitization study in guinea pigs, a phototoxicity study in rabbits, and repeat dose dermal toxicity studies in minipigs.

Econazole nitrate 1% foam did not induce dermal irritation in rabbits. No skin sensitization or phototoxicity was noted for econazole nitrate 1% foam, in guinea pigs and rabbits, respectively.

Based on the Agency's finding of safety for the listed drug and the conducted nonclinical studies with econazole nitrate foam, overall the nonclinical review concludes that there is no significant safety concern for Ecoza (econazole) topical Foam 1%, at the proposed clinical dose.

The nonclinical review by Dr. Jerry Wang concludes that the application is approvable from a pharmacology/toxicology perspective. There are no outstanding nonclinical issues and no recommended post marketing requirements.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Dr. Chinmay Shukla, who noted no approvability issues for the application, but recommends post marketing requirements for the assessment of drug interactions.

The applicant conducted PK assessment in the following trials, which construct the clinical bridge to the referenced econazole cream product:

- D79-2902-07: Phase 2 safety and efficacy trial in adults with interdigital and/or moccasin type tinea pedis
- 0792951-109: Phase 2 pediatric PK trial (12-17 year old) in subjects with interdigital tinea pedis
- 0792951-303: Phase 3 safety and efficacy trial

Dr. Shukla's review concludes that the AUC for the foam formulation is slightly higher than the cream formulation, and that pediatric subjects had slightly higher exposure than adults with the foam formulation.

His review notes that in adult subjects, the 90% confidence interval (CI) of the ratio of geometric means of AUC (0.73 to 1.87) and C_{max} (0.74 to 1.46) of Foam vs. Cream were outside the no effect range of 0.8 to 1.25, suggesting that the Foam and the Cream are not bioequivalent. Based on ratio of geometric mean values, the C_{max} of econazole appear to be similar (observed point estimate = 1.04), however, the exposure (AUC) of econazole following administration of the Foam formulation appears to be ~ 17% higher than the Cream (observed point estimate = 1.17).

In pediatric subjects (12-17 years) limited PK samples were obtained. The systemic econazole concentrations (geometric mean) appear to be approximately 2 fold higher at 7 h and 11 h post-dose following administration of the Foam formulation compared to the Cream.

Based on cross trial comparison, the geometric mean concentrations of econazole at 7 h and 11 h post-dose in pediatric subjects was ~ 1.7 and ~ 1.2 fold higher, respectively, than the 8 h and 12 h post-dose concentrations in adults, following administration of the Foam formulation.

Based on the PK results of Trial D79-2902-07 (PK trial in adults), the applicant requested a waiver to conduct QT/QTc evaluations. Despite the slightly higher exposure, the review team notes the long history of econazole use in addition to the lack of QT related adverse events reported, and concludes that the waiver for conducting TQT assessment appears reasonable.

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.

As the current Spectazole Cream label dates from 1982, and thus includes no drug interaction information, Section 7 – Drug Interactions will be a novel addition to the prescribing information. (The owner of Spectazole Cream has been requested to add similar labeling in order to support additions to multiple generic labels as well.)

Since there have been no studies conducted to evaluate the drug interaction potential of econazole, the review team recommends that this applicant should be requested to assess in vitro drug interaction potential as post marketing requirements (PMR's). Based on the in vitro results, the need for further in vivo assessments and appropriateness for labeling will be evaluated at that time.

These recommended PMR 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.

The applicant received the following and a response is pending as of the date of this review:

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.

There are no outstanding issues from the clinical pharmacology perspective beyond agreement on the above PMR's.

6. Clinical Microbiology

No critical issues were identified during the review cycle by the clinical microbiology reviewer, Dr. Shukal Bala.

Econazole is an imidazole antifungal and drugs in this class act by inhibiting the biosynthesis of ergosterol which is a constituent of fungal cell membranes. Ergosterol serves as a bioregulator of membrane fluidity and is responsible for membrane integrity of in fungal cells.

T. rubrum was the most common dermatophyte isolated. Econazole nitrate was deemed effective in patients with infections due to *T. rubrum*, *T. mentagrophytes*, and *E.floccosum.*

The applicant proposes to label Ecoza Foam, 1% (b) (4) However, in addition to tinea pedis, econazole nitrate cream is approved for the treatment of tinea cruris and tinea corporis, cutaneous candidiasis and in the treatment of tinea versicolor. The applicant is seeking approval of Econazole Nitrate Foam, 1% for the treatment of interdigital tinea pedis only. Since the indication for the foam differs substantially from that of the referenced product, recommended labeling is limited to the microorganisms typically associated as being causative for interdigital tinea pedis.

Pending acceptance of the labeling, there are no outstanding issues related to clinical microbiology.

7. Clinical/Statistical- Efficacy

The applicant submitted substantial evidence that econazole nitrate foam 1% was superior to its vehicle in the treatment of interdigital tinea pedis in two studies. The studies enrolled subjects age 12 and older with a clinical diagnosis of interdigital tinea pedis involving at least two web spaces (at least moderate scaling and mild erythema) and positive KOH microscopy and a positive fungal culture.

Study 302 was a two-arm study (econazole foam vs. vehicle foam). Study 303 was a four-arm study (econazole foam, vehicle foam, econazole cream, and vehicle cream). Study 303 included an econazole cream arm as one component of the clinical bridge to the Agency's findings of safety for econazole cream for this 505(b)(2) application. The vehicle cream arm was included to maintain blinding. Subjects were treated once daily for four weeks. Both protocols were reviewed under Special Protocol Assessments and agreements were reached on the study design and endpoints.

The primary efficacy endpoint in both studies was complete cure (scores of 0 [none] on all signs and symptoms, as well as negative KOH microscopy and negative culture) at Day 43, two weeks after the end of treatment. The secondary endpoints were mycological cure (negative KOH and negative culture) and effective treatment (no or mild erythema and/or scaling [scores of 0 or 1] with all other signs and symptoms absent [scores of 0], negative KOH, and negative culture) at Day 43.

The primary and secondary efficacy endpoints for econazole foam versus vehicle foam were all statistically significant at Day 43. The efficacy outcomes are summarized in **Table 1** as provided by the Agency Statistical Reviewer, Dr. Kathleen Fritsch.

Table 1 – Efficacy Results in Studies 302 and 303 (MITT)

Study 302	Econazole Foam N=82	Vehicle Foam N=83			P-value
Complete Cure	19 (23%)	2 (2%)			<0.001
Effective Treatment	40 (49%)	9 (11%)			<0.001
Mycological Cure	56 (68%)	13 (16%)			<0.001
Study 303	Econazole Foam N=91	Vehicle Foam N=83	Econazole Cream N=52	Vehicle Cream N=30	P-value[1]
Complete Cure	23 (25%)	4 (5%)	17 (33%)	1 (3%)	<0.001
Effective Treatment	44 (48%)	9 (11%)	27 (52%)	1 (3%)	<0.001
Mycological Cure	61 (67%)	15 (18%)	33 (63%)	1 (3%)	<0.001

[1] P-value of econazole foam versus vehicle foam. All p-values are from the CMH test stratified on analysis center.

Treatment effects were generally consistent across subgroups and centers. The conclusions were consistent across various assumptions regarding missing data, although many of the applicant's sensitivity analyses led to larger estimated treatment effects than the primary method of LOCF. However, Dr. Fritsch's post-hoc analyses that treated the missing data in a conservative manner indicated that the treatment effect was robust for the handling of missing data.

Treatment effects were generally consistent across gender, race, age and country subgroups, although some subgroups were small. The majority of subjects had baseline cultures with *T. rubrum*, though smaller numbers of subjects had baseline cultures with *E. floccosum, T. mentagrophytes, T. tonsurans*, or mixed pathogens. Treatment effects were generally consistent across the baseline pathogens, noting that all pathogens except *T. rubrum* had small sample sizes.

While only four adolescent subjects were included in the MITT population comparison (two for econazole foam and two for vehicle foam), it is reasonable to extrapolate efficacy to age 12 based on the adult experience in this development program and the history of econazole cream use since 1982. The disease characteristics of interdigital tinea pedis do not significantly differ between adolescents and adults.

The clinical and biostatistical reviewers concur that adequate evidence of efficacy has been presented in the application and there are no outstanding issues in this regard. Applicant concurrence with labeling is pending as of the date of this review.

8. Safety

The development program for econazole foam included 698 subjects. No deaths, pregnancies or treatment-related SAEs were reported in subjects treated with econazole nitrate foam.

Similar proportions of econazole foam and vehicle foam subjects experienced adverse events during the study (13% vs. 12% respectively in Study 302 and 10% vs. 10% in Study 303). Few adverse events occurred in more than one subject per arm, and those that did (headache and nasopharyngitis) generally occurred in similar rates on all treatment arms. Two events were classified as probably or definitely related to treatment: application site dermatitis and application site pain. Both of these events occurred in vehicle foam subjects. No significant adverse events were deemed related to econazole foam by either the applicant, or Agency reviewers.

The relative safety seen in the development program will be acknowledged by the following in product labeling:

> "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 Warnings and Precautions section of the prescribing information only comments on the flammability of the foam product:

> "Ecoza topical foam is flammable. Avoid heat, flame, and smoking during and immediately following application. Contents under pressure. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C) even when empty. Do not store in direct sunlight."

No clinically meaningful changes in laboratory monitoring were noted in the development program, nor were any electrocardiographic changes noted in a subset of 98 subjects.

Provocative dermal safety studies did not identify any issues with sensitization, phototoxicity, or photoallergenicity. No irritation signal was noted in the cumulative irritation study, and no labeling information is recommended beyond the potential for local skin reactions as noted in the pivotal clinical trials.

No additional data was submitted in the 120 day safety update.

There are no significant safety issues with this product, and labeling is adequate to communicate the limited concerns regarding potential adverse reactions. There are no remaining safety issues pending for this application.

9. Advisory Committee Meeting

The review team determined early in the application review cycle that this azole antifungal presented no novel or complex regulatory issues that required the input of an advisory committee. Econazole has a thirty year marketing history, and there were no concerns related to primary safety or efficacy determinations, or other regulatory issues.

10. Pediatrics

The Sponsor has 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, though pediatric subjects were small.

For subjects 11 years of age and younger, the applicant requested a partial waiver of pediatric studies. At a meeting with the Pediatric Review Committee (PeRC) on 05/29/2013, PeRC agreed to the Sponsor's partial waiver request because studies are impossible or highly impracticable in this indication.

The recommended indication for this product is for treatment of interdigital tinea pedis in patients 12 years of age and older.

11. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application.

GMP inspections are complete, and there are no outstanding issues impacting approval from the Office of Compliance. The Office of Compliance has made an overall "Acceptable" recommendation for the facilities involved in this NDA.

Following preliminary review of the data in the application by the team, and in light of the 30 years of marketing experience for the active moiety, econazole, no study sites were recommended for DSI inspection for this application. Review of the clinical data did not identify any study sites that warranted inspection.

12. Labeling

The trade name of "Ecoza" has been accepted by DMEPA. The ONDQA recommendation is to add "topical" to the name of the product in labeling in accordance with recent USP

recommendations to minimize dosage form confusion. The name of the product in labeling will be "Ecoza topical foam, 1%".

Review of the proposed label submitted by the applicant was based on evaluation of the clinical trials for the NDA as well as DMEPA, DRISK, and DDMAC consultative reviews.

Labeling is adequate to communicate necessary safety information to prescribers. Final agreement on Agency proposed labeling, including carton/container labeling, is pending as of the date of this CDTL review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The conclusion of the clinical review, and that of the review team, concurred by this CDTL review, is that safety and efficacy of econazole foam 1% for interdigital tinea pedis is supported by the clinical development program. An approval action is recommended pending successful completion of labeling negotiations.

- Risk Benefit Assessment

Efficacy for interdigital tinea pedis has been adequately demonstrated by the applicant. The safety findings are uncommon and largely limited to local adverse events, with no serious adverse events deemed related to the proposed topical foam product.

The benefits of this product outweigh the risks when used as the prescribing information recommends, and this CDTL review concurs that this application should be approved. The conclusion that this application should be approved is shared by each review discipline, and there are no outstanding approvability issues beyond labeling.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

REMS is neither required nor recommended for this topical antifungal product. Labeling is adequate to inform prescribers and patients of expected adverse events and risks.

- Recommendation for other Postmarketing Requirements and Commitments

The rationale for the recommended PMR/PMC's is described above in the section related to clinical pharmacology. The review team recommends these as FDAAA related safety issues. The recommended PMR/PMC's to convey to the applicant are:

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.

- Recommended Comments to Applicant

There are no other recommended comments beyond the PMR/PMC's listed above and draft labeling which will be conveyed to the applicant.

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/s/

DAVID L KETTL
09/30/2013