

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205175Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 205175
Supporting document/s: SD 1
Applicant's letter date: 12/22/2012
CDER stamp date: 12/26/2012
Product: ECOZA (econazole nitrate) Foam, 1%
Indication: Tinea pedis
Applicant: AmDerma Pharmaceuticals, Bridgewater, NJ
Review Division: Dermatology and Dental Products
Reviewer: Jianyong Wang, PhD
Supervisor/Team Leader: Barbara Hill, PhD
Division Director: Susan Walker, MD
Project Manager: Matthew White

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205175 are owned by AmDerma Pharmaceuticals or are data for which AmDerma Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 205175 that AmDerma Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205175.

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	3
1.1	INTRODUCTION	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	3
1.3	RECOMMENDATIONS	4
2	DRUG INFORMATION	6
2.1	DRUG	6
2.2	RELEVANT INDS, NDAs, BLAs AND DMFs	6
2.3	DRUG FORMULATION	6
2.4	COMMENTS ON NOVEL EXCIPIENTS	7
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	7
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	8
2.7	REGULATORY BACKGROUND	8
3	STUDIES SUBMITTED.....	9
3.1	STUDIES REVIEWED.....	9
3.2	STUDIES NOT REVIEWED	9
3.3	PREVIOUS REVIEWS REFERENCED.....	10
4	PHARMACOLOGY	10
4.1	PRIMARY PHARMACOLOGY	10
4.2	SECONDARY PHARMACOLOGY	10
4.3	SAFETY PHARMACOLOGY	10
5	PHARMACOKINETICS/ADME/TOXICOKINETICS	10
5.1	PK/ADME.....	10
5.2	TOXICOKINETICS	11
6	GENERAL TOXICOLOGY.....	11
6.1	SINGLE-DOSE TOXICITY	11
6.2	REPEAT-DOSE TOXICITY	11
7	GENETIC TOXICOLOGY	17
8	CARCINOGENICITY	17
9	REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY	17
10	SPECIAL TOXICOLOGY STUDIES.....	18
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	19
12	APPENDIX/ATTACHMENTS.....	21

1 Executive Summary

1.1 Introduction

The sponsor submitted a 505(b)(2) NDA to pursue marketing approval of ECOZA Foam, 1%, for the treatment of tinea pedis. The sponsor intends 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 clinical bridging studies.

1.2 Brief Discussion of Nonclinical Findings

Econazole nitrate is an azole antifungal and has broad-spectrum antifungal activities. The sponsor proposed to rely upon the Agency's finding of safety for the reference listed drug Spectazole[®] Cream, 1%, to support some nonclinical portions of this 505(b)(2) application. In addition to relying upon the Agency's finding of safety for the listed drug, the sponsor also 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.

Topical doses up to 4% econazole nitrate foam were tested in a 4-week dermal minipig study and topical doses up to 2% foam were tested in a 13-week dermal minipig study. In both studies there were no significant treatment-related effects on body weight, ophthalmology, ECG, hematology, clinical chemistry, gross pathology, or histopathology. Slight dermal irritation was noted in animals treated with 4% or 2% foam. The multiples of human exposure based on AUC comparison between the NOAEL identified in the 13-week minipig study and the maximum clinical dose are 27.

According to summary information from literature, econazole nitrate was negative in the Ames test and did not induce structural chromosome aberration in vivo. The result of in vivo micronucleus test(s) was inconclusive (either contradictory results or insufficient data). The results of in vivo aneuploidy tests were also inconclusive. Econazole nitrate is a suspected aneugen. The human risk related to inconclusive aneuploidy tests is not clear. Carcinogenicity data are not available for econazole nitrate.

Oral administration of econazole nitrate in rats has been reported to produce prolonged gestation. Econazole nitrate has not been shown to be teratogenic when administered orally to mice, rabbits or rats. Fetotoxic or embryotoxic effects were observed in Segment I oral studies with rats receiving 10 to 40 times the human dermal dose.

Similar effects were observed in Segment II or Segment III studies with mice, rabbits and/or rats receiving oral doses 80 or 40 times the human dermal dose.

Following oral administration of econazole nitrate to lactating rats, econazole and/or metabolites were excreted in milk and were found in nursing pups. Also, in lactating rats receiving large oral doses (40 or 80 times the human dermal dose), there was a reduction in post-partum viability of pups and survival to weaning; however, at these high doses, maternal toxicity was present and may have been a contributing factor.

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

1.3 Recommendations

1.3.1 Approvability

NDA 205175 for ECOZA (econazole nitrate) Foam, 1% is approvable from a pharmacology/toxicology perspective, provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the ECOZA Foam label.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the ECOZA Foam label reproduced below. The pharmacologic class designation for econazole nitrate is azole antifungal. This is an established pharmacologic class.

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

ECOZA Foam is ^{(b) (4)} an azole antifungal indicated for the treatment of interdigital tinea pedis ^{(b) (4)}

^{(b) (4)}

8.1 Pregnancy

(b) (4) Pregnancy Category C

There are no adequate and well-controlled (b) (4) in pregnant women. (b) (4) should be used (b) (4) during pregnancy only if the potential benefit justifies the potential risk to the fetus (b) (4)

Econazole nitrate has not been shown to be teratogenic when administered orally to mice, rabbits or rats. Fetotoxic or embryotoxic effects were observed in Segment I oral studies with rats receiving 10 to 40 times the human dermal dose. Similar effects were observed in Segment II or Segment III studies with mice, rabbits and/or rats receiving oral doses 80 or 40 times the human dermal dose.

8.3 Nursing Mothers

It is not known whether econazole nitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when econazole nitrate is administered to a nursing woman. Following oral administration of econazole nitrate to lactating rats, econazole and/or metabolites were excreted in milk and were found in nursing pups. (b) (4)

(b) (4)

12.1 Mechanism of Action

ECOZA Foam is an azole antifungal [see Clinical Pharmacology (12.4)].

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4) Long-term animal studies to determine the carcinogenic potential of ECOZA Foam have not been performed.

Oral administration of econazole nitrate in rats has been reported to produce prolonged gestation. (b) (4)

Note:

The addition of the second sentence in Section 8.3, the deletion (b) (4) and the deletion (b) (4) are recommended by the clinical reviewer.

2 Drug Information

2.1 Drug

CAS Registry Number: 24169-02-6

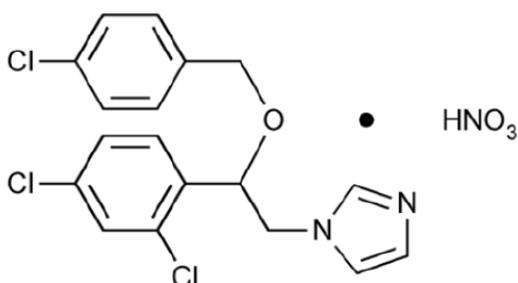
Generic Name: Econazole nitrate

Code Name: None

Chemical Name: 1-[2-((4-chlorophenyl) methoxy)-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole mononitrate

Molecular Formula/Molecular Weight: $C_{18}H_{15}Cl_3N_2O \cdot HNO_3$ / 444.7

Structure:



Pharmacologic Class: azole antifungal

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 18751 Spectazole[®] (econazole nitrate) Cream 1%, approved on 12/23/1982, discontinued, by Ortho Jassen

ANDA 76075 Econazole nitrate cream 1%, approved on 11/26/2002, by Fougera

IND 77523 Econazole nitrate foam 1%, by AmDerma Pharmaceuticals, DDDP

2.3 Drug Formulation

The composition of ECOZA (econazole nitrate) Foam, 1% is listed in the following table.

Component	(b) (4)
Econazole nitrate USP	
Purified water	
Stearic acid NF	
(b) (4)	
Povidone USP)	
Propylene glycol USP	
Glycerin (b) (4) USP	
Dimethicone (b) (4) NF	
Trolamine (b) (4) NF	
Polysorbate 20 NF	

The propellant for this foam is n-butane.

2.4 Comments on Novel Excipients

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.

2.5 Comments on Impurities/Degradants of Concern



2. The container closure system for ECOZA Foam 1%

The chemistry review team expressed their concern regarding the container closure system for ECOZA Foam because for certain components there were insufficient data or some tests for extractables did not meet the assay criteria (refer to the chemistry review for this NDA).

From a pharmacology/toxicology perspective, the safety concern for the leachables from the drug container closure system is not significant, based on the following considerations.

- ECOZA Foam is a topical drug product applied to a small skin area (interdigital area) with a relatively short treatment duration. The dermal absorption of ECOZA Foam 1% is very limited; therefore the exposure to leachables from the drug container closure system would be very minimal.
- Extraction tests were conducted in extreme conditions (b) (4). Therefore extractables from such tests may not exist in actual use of the drug product (the leachable tests were not conducted for this container closure system).
- All the components of the container closure system, (b) (4) have 21 CFR compliance references (b) (4). Systemic exposure to leachables from food packaging is presumably much higher than that from the container closure system for ECOZA Foam, considering large quantity of food consumption via oral route.

2.6 Proposed Clinical Population and Dosing Regimen

Clinical population: Patients with interdigital tinea pedis, 12 years of age and older.

Dosing regimen: Applied to cover affected areas, once daily for 4 weeks.

The mean daily topical dose that has been tested in two maximum use clinical PK trials was 2.39 g and 3.20 g ECOZA Foam, 1%, in adult and pediatric subjects, respectively (per e-mail communication with Dr. Chinmay Shukla, the clinical pharmacology reviewer). In the two PK trials, the mean daily topical dose of the comparator, econazole nitrate cream 1%, was slightly higher than the dose of ECOZA Foam (dose of the 1% cream: 2.90 and 3.89 g/day in adult and pediatric subjects, respectively).

2.7 Regulatory Background

IND 77523 was initially opened by Quinnova Pharmaceuticals and subsequently transferred to AmDerma Pharmaceuticals. The sponsor pursues the marketing approval of ECOZA Foam, 1%, through the 505(b)(2) regulatory pathway. The sponsor proposed to rely upon the Agency's finding of safety and effectiveness for Spectazole[®] (econazole nitrate) Cream, 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 clinical bridging studies.

The following meetings have been conducted:

- PreIND meeting, 09/10/2007
- End of Phase 2 meeting, 04/15/2009
- Guidance meeting, 04/14/2010
- PreNDA meeting, 08/29/2012

3 Studies Submitted

3.1 Studies Reviewed

Pharmacokinetic studies:

1. Method for the determination of econazole in minipig plasma using high-performance liquid chromatography with ultraviolet (UV) detection (Study# MN07107-03)
2. Validation of a method for the determination of econazole in minipig plasma using high-performance liquid chromatography with ultraviolet (UV) detection (Study# MC07B-0214)
3. Validation of a method for the determination of econazole in minipig plasma using high-performance liquid chromatography with mass spectrometric detection (Study# MC11B-0088-01)

Repeat Dose Toxicology Studies:

1. Econazole Nitrate 1%: A 4-week dermal toxicity study in Gottingen minipigs. (Study# 1246-005)
2. Econazole nitrate placebo foam: a pilot dermal toxicity study in Gottingen minipigs (Study# 1606-002)
3. Econazole nitrate foam: a 13-week dermal toxicity study with a 4-week recovery period in Gottingen minipigs (Study# 1606-003)

Special toxicology studies:

1. Primary dermal irritation study in rabbits (Study# 0420LT28.008)
2. Dermal contact hypersensitivity in guinea pigs (Buehler Method) (Study# 0424GT28.004)
3. Phototoxicity test in rabbits (Study# 0432LT28.002)

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

- Nonclinical review, IND 77523, by Dr. Carmen Booker, dated 03/06/2008

4 Pharmacology

4.1 Primary Pharmacology

A number of literature reviews were included in the NDA submission to provide summary information regarding econazole nitrate's antifungal activity. Econazole nitrate is an imidazole, which belongs to the pharmacologic class of azole antifungal.

Econazole nitrate has exhibited broad-spectrum antifungal activity against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Microsporum canis*, *Microsporum audouini*, *Microsporum gypseum*, *Epidermophyton floccosum*, *Candida albicans* and *Malassezia furfur*. It also has antimicrobial activity against certain gram positive bacteria.

Econazole nitrate is believed to exert its antifungal activity by altering fungal cell membrane and interfering with intracellular enzymes. For imidazoles, inhibition of ergosterol synthesis by blocking C-14 demethylation has been proposed as the mechanism of action. Ergosterol is a critical component of fungal cell membrane. Decrease of ergosterol in fungal membrane disrupts the structure and many functions of fungal membrane leading to inhibition of fungal growth.

Literature also suggested that at high concentrations, imidazoles may also exert a fungicidal effect by rapid damage to fungal membranes. This was indicated by increased membrane permeability in both non-growing and growing fungal cells.

4.2 Secondary Pharmacology

None.

4.3 Safety Pharmacology

No stand-alone safety pharmacology studies were submitted to the NDA. ECG was examined in both the 4-week and 13-week dermal minipig studies and no treatment-related effects were observed.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No PK studies were submitted to the NDA. The sponsor has developed and validated two bioanalytical methods to quantify econazole nitrate in minipig plasma samples

collected in repeat dose dermal minipig studies for TK analysis. The first method (HPLC/UV detection), used in the 4-week minipig study, has a lower limit of quantification of 20 ng/ml and the method was linear through 1000 ng/ml. The second method (HPLC/MS detection), used in the 13-week minipig study, has a lower limit of quantification of 0.1 ng/ml and the method was linear through 50 ng/ml.

According to Dr. Chinmay Shukla, the clinical pharmacology reviewer, in maximum use clinical PK trials, the mean exposure (AUC) of ECOZA Foam 1% was higher than the comparator econazole nitrate 1% cream. After 29 days of once daily topical administration in adult subjects (mean daily topical doses were 2.39 g and 2.90 g for 1% foam and 1% cream, respectively), mean C_{max} values were 417 and 344 pg/ml and mean AUC_{0-12} values were 3440 and 2520 pg•hr/ml, for 1% foam and 1% cream, respectively.

Reviewer's comments:

It appeared that the bioavailability of 1% foam was higher than that of 1% cream. Per the communication with the clinical review team, since the safety profile for ECOZA Foam 1% was similar to that for the comparator (1% cream) in clinical bridging studies, it is acceptable for the sponsor to rely upon the Agency's finding of safety for the listed drug.

Because AUC values for reproductive and developmental toxicology studies were not presented in the Spectazole[®] Cream label, human multiples based on AUC comparison could not be provided for the ECOZA Foam label. The human multiples presented in the Spectazole[®] Cream label were based on topical dose comparison. The sponsor proposed to use the same human multiples in the description of reproductive and developmental toxicology studies in the ECOZA Foam label. Considering the mean clinical topical doses for 1% foam and 1% cream were generally comparable in clinical PK trials, the sponsor's proposal is considered acceptable.

5.2 Toxicokinetics

Included in toxicology studies.

6 General Toxicology

6.1 Single-Dose Toxicity

None.

6.2 Repeat-Dose Toxicity

Study #1

Econazole Nitrate 1%: A 4-week dermal toxicity study in Gottingen minipigs (Study# 1246-005, refer to the review for IND 77523, by Dr. Booker, 03/06/2008)

Topical doses of 0 (vehicle), 1%, and 4% econazole nitrate foam were applied to ~200 cm² skin area of minipigs (3/sex/group), twice daily (6 hr apart) for 4 weeks (4 mg/cm²/dose, ~800 mg foam per application, ~1.1 and 4.6 mg/kg/day econazole nitrate for a 14 kg minipig). The vehicle composition was not described in the study report. No mortality was noted. A slight increase in erythema was noted in high dose animals. No test article-related effects on body weight, ophthalmology, ECG, hematology, clinical chemistry, gross pathology, organ weights, or histopathology were noted. TK analysis was not performed as drug concentrations in all plasma samples were below detection limit (20 ng/ml). The NOAEL was considered the high dose, 4% foam applied twice daily for 4 weeks.

Study #2

Econazole nitrate placebo foam: a pilot dermal toxicity study in Gottingen minipigs (Study# 1606-002)

This pilot study was conducted to determine the maximum feasible dose volume for a subsequent 13-week dermal toxicity study. Econazole nitrate foam vehicle (clinical formulation) was administered to three male and three female minipigs. On Day 1, dose volumes of 1000 and 250 mg/kg were tested (one animal for each dose). For the remaining four animals, a dose volume of 100 mg/kg was administered on Day 1. Thereafter, 100 mg/kg foam vehicle was administered to all animals on Days 2, 5, 6, 7, 8, 9, 12, 13, and 14. At 1000 mg/kg, significant amount of foam vehicle remained on the application site for several hours postdose and some of the material was rubbed off on the cage. A similar situation was observed with the 250 mg/kg, although to a lesser extent. The dose levels of 1000 and 250 mg/kg were considered excessive. The application of econazole nitrate foam vehicle at 100 mg/kg was well tolerated in this study. Based on the study results, a dose volume of 100 mg/kg will be used in the 13-week dermal minipig study as the maximum feasible dose volume of the econazole nitrate foam formulation.

Study #3

Study title: Econazole nitrate foam: a 13-week dermal toxicity study with a 4-week recovery period in Gottingen minipigs

Study no.:	1606-003
Study report location:	SD 1, Module 4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10/10/2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Econazole nitrate foam vehicle, lot # CIE-C Fougera Econazole Nitrate Cream 1%, lot # 049K, 739K, and 136M Econazole nitrate foam 0.5%, lot # DLA Econazole nitrate foam 1%, lot # CIF-1C Econazole nitrate foam 2%, lot # DGR

Key Study Findings

Two low dose males were euthanized one day before the scheduled necropsy. Their moribundity was not considered test article-related. Very slight dermal irritation was noted in animals treated with 2% econazole nitrate foam. Fougera Econazole Nitrate Cream 1% was also tested in this study as a reference drug. No significant toxicity was noted in this study. When comparing the 1% cream and 1% foam exposures, it appeared that the absorption of econazole nitrate was more efficient from the 1% foam.

The NOAEL was identified as the high dose in this study, 2 mg/kg/day (2% foam applied at 100 mg/kg/day), at which the Day 90 AUC₀₋₂₄ values were 102 and 92 ng•hr/ml, in males and females, respectively.

Methods

Doses:	0 (untreated), 0 (vehicle), 0.5, 1, and 2 mg/kg/day (0.5%, 1%, and 2% foam) (per the sponsor 2% is the maximum concentration of econazole nitrate that is soluble in the foam formulation)
Frequency of dosing:	Once daily
Route of administration:	Dermal (applied to ~10% BSA)
Dose volume:	100 mg/kg (the maximum feasible dose volume)
Formulation/Vehicle:	Vehicle composition was not described in this study report. However, the lot number indicates that the vehicle is the clinical formulation.
Species/Strain:	Gottingen minipigs
Number/Sex/Group:	4/sex/group for main study
Age:	4-5 months
Weight:	Male 7.9-13.4 kg, female 8.7-12.8 kg
Satellite groups:	recovery animals: 2/sex/group for all groups except the untreated control group
Unique study design:	Fougera Econazole Nitrate Cream 1% was also tested in a separate group in this study as a reference drug, with a dose volume of 6 mg/cm ² applied to 10% BSA (~2.3 mg/kg econazole nitrate on Day 90)
Deviation from study protocol:	None remarkable

Observations and Results

Mortality

Two low dose male minipigs were euthanized on Day 91 (one day before the scheduled necropsy). The cause of moribundity was related to lung inflammation/necrosis. Significant microscopic findings in the lungs of the two animals included hemorrhage, edema, subacute/chronic inflammation, and necrosis. Because there were no similar findings in any other groups, the lung inflammation/necrosis was not dose-related and considered incidental and unrelated to econazole nitrate administration.

Clinical Signs

No significant treatment-related clinical signs were noted. Decreased activity was observed in the two moribund animals. Abrasions, skin discolorations (red/brown), and scabbing were observed occasionally in all groups and were not considered test article-related. Dermal irritation scores were recorded during the study (see the copied table from submission below). An increase in the incidence of Grade 1 erythema was observed during the treatment period at high dose, indicating very slight dermal irritation caused by 2% econazole nitrate foam.

Incidence Count by Erythema Grade										
Group*	Males					Females				
	0	1	2	3	4	0	1	2	3	4
Untreated Control	76	0	0	0	0	75	1	0	0	0
Placebo	110	4	0	0	0	114	0	0	0	0
Reference Drug	110	3	0	1	0	111	3	0	0	0
Econazole 0.5%	104	8	0	0	0	114	0	0	0	0
Econazole 1%	110	4	0	0	0	109	5	0	0	0
Econazole 2%	99	15	0	0	0	91	23	0	0	0

*Untreated control groups had 4 animals/sex, whereas all other groups had 6 animals/sex

Erythema Grades:
 0 - No erythema
 1 - Very slight erythema (barely perceptible)
 2 - Well-defined erythema
 3 - Moderate to severe erythema
 4 - Severe erythema (beet redness) to slight eschar formation (injuries in depth)

Body Weights

No significant treatment-related effects were noted.

Ophthalmology

Ophthalmoscopy was examined pretest and prior to scheduled necropsy. No significant treatment-related effects were noted.

ECG

ECG was measured pretest and at predose and 1 hr postdose during the last week of dosing. Heart rate, RR, PR, QT intervals, and QRS duration were measured. QTc interval was calculated. No significant test article-related effects were noted.

Hematology and Coagulation

No significant treatment-related effects were noted.

Clinical Chemistry

No significant treatment-related effects were noted.

Gross Pathology

Scheduled necropsy was conducted on Day 92 (main study) and Day 120 (recovery animals). No significant treatment-related findings were noted.

Organ Weights

The following organs were weighed: adrenal gland, brain, epididymis, heart, kidney, liver, lung, ovary, pituitary gland, prostate gland, salivary gland (submandibular), spleen, testis, thymus, and thyroid.

No significant treatment-related changes were noted in animals in scheduled necropsy.

Histopathology

Adequate Battery: Yes.

All tissues and organs collected at necropsy from all animals were processed and examined microscopically.

Tissue list: adrenals, aorta, bone with marrow (femur, sternum, and rib), brain, cecum, colon, duodenum, epididymis, esophagus, eyes, gallbladder, gut associated lymphoid tissue (GALT), heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, lymph node (mandibular and mesenteric), mammary gland, optic nerve, ovaries, pancreas, pituitary, prostate, rectum, salivary gland (mandibular, parotid, and sublingual), sciatic nerve, seminal vesicle, skeletal muscle, skin (treated and untreated), spinal cord, spleen, stomach, testes, thymus, thyroids, tongue, trachea, ureter, urinary bladder, uterus and vagina.

Peer Review: No.

Histological Findings:

There were no significant treatment-related findings in scheduled necropsy (terminal or recovery animals).

Toxicokinetics

The TK blood samples were collected on Days 1 and 90. Due to an insufficient number of samples with measureable concentrations of econazole nitrate on Day 1, TK parameters could not be calculated for Day 1. The TK parameters for Day 90 are presented in the following table.

TK parameters (mean values) for Day 90:

	1% cream		0.5% foam		1% foam		2% foam	
	Male	Female	Male	Female	Male	Female	Male	Female
C_{max} (ng/ml)	3.01	3.24	1.30	1.85	2.17	2.48	5.22	4.52
T_{max} (hr)	1.83	4.00	3.00	7.33	6.00	4.33	3.67	4.67
AUC_{0-24} (ng•hr/ml)	55.9	59.1	24.9	38.9	45.5	48.8	102	92.3

With repeat dosing, the mean values of C_{max} and AUC_{0-24} increased with dose in an approximately dose-proportional manner. When comparing the 1% cream and 1% foam exposures, it appeared that the absorption of econazole nitrate was more efficient from

the 1% foam (AUC values were slightly higher in the 1% cream group while the dose for 1% cream was 2.3x the dose for 1% foam). A slight gender difference was noted only at 0.5%, where systemic exposure was higher in females than in males.

Dosing Solution Analysis

Not conducted. Test articles were provided by the sponsor.

7 Genetic Toxicology

No genetic toxicology studies were submitted to the NDA. The sponsor provided a brief summary for the genotoxicity information of econazole nitrate (obtained from the published literature: Aardema et al. 1998. Aneuploidy: a report of an ECETOC task force. *Mutat Res* 410:3-79). Econazole nitrate was negative in the Ames test and did not induce structural chromosome aberration in vivo. The result of in vivo micronucleus test(s) was inconclusive (either contradictory results or insufficient data). The results of in vivo aneuploidy tests using male germ cells or somatic cells were also inconclusive. Econazole nitrate is a suspected aneugen. The human risk related to inconclusive aneuploidy tests is not clear.

No genetic toxicology information for econazole nitrate was presented in the Spectazole[®] Cream label. The summary the sponsor obtained from literature does not contain detailed information which allows an in-depth review. Therefore, such summary information will not be included in the ECOZA Foam label.

8 Carcinogenicity

No carcinogenicity data were submitted to the NDA. The following wording is contained in the Spectazole[®] Cream label.

“Carcinogenicity Studies: Long-term animal studies to determine carcinogenic potential have not been performed.”

9 Reproductive and Developmental Toxicology

The following wording is contained in the Spectazole[®] Cream label.

“Fertility (Reproduction): Oral administration of econazole nitrate in rats has been reported to produce prolonged gestation. Intravaginal administration in humans has not shown prolonged gestation or other adverse reproductive effects attributable to econazole nitrate therapy.

Pregnancy: Pregnancy Category C. Econazole nitrate has not been shown to be teratogenic when administered orally to mice, rabbits or rats. Fetotoxic or embryotoxic effects were observed in Segment I oral studies with rats receiving 10 to 40 times the human dermal dose. Similar effects were observed in Segment II or Segment III studies

with mice, rabbits and/or rats receiving oral doses 80 or 40 times the human dermal dose.

Econazole nitrate should be used in the first trimester of pregnancy only when the physician considers it essential to the welfare of the patient. The drug should be used during the second and third trimesters of pregnancy only if clearly needed.

Nursing Mothers: It is not known whether econazole nitrate is excreted in human milk. Following oral administration of econazole nitrate to lactating rats, econazole and/or metabolites were excreted in milk and were found in nursing pups. Also, in lactating rats receiving large oral doses (40 or 80 times the human dermal dose), there was a reduction in post partum viability of pups and survival to weaning; however, at these high doses, maternal toxicity was present and may have been a contributing factor. Caution should be exercised when econazole nitrate is administered to a nursing woman.”

The sponsor also provided very brief summary information regarding reproductive and developmental toxicity of econazole nitrate, which was obtained from literature. However, such information does not allow an in-depth review and therefore could not be presented in the drug label. Because this NDA is a 505(b)(2) application, the sponsor can rely upon the Agency’s finding of safety for the listed drug Spectazole[®] Cream, as reflected in the Spectazole[®] Cream label. As discussed in Section 5.1, the human multiples described in the Spectazole[®] Cream label will remain the same for the ECOZA Foam label.

10 Special Toxicology Studies

1. Primary dermal irritation study in rabbits (Study# 0420LT28.008)

A single dose of 0.5 ml econazole nitrate 1% foam (Lot# QEN 701-1) was applied to intact skin of 3 male New Zealand White rabbits under occlusion for 4 hours. The foam composition was not described in the study report. At the end of the exposure period, test sites were wiped with water and gauze. Test sites were evaluated at 4, 24, 48 and 72 hours after patch removal. No dermal irritation was noted in this study.

2. Dermal contact hypersensitivity in guinea pigs (Buehler Method) (Study# 0424GT28.004)

For the induction phase of this study, guinea pigs (10/sex) were treated once weekly for 3 weeks with 6-hour occluded dermal applications of econazole nitrate 1% foam (Lot# QEN 701-1). The foam composition was not described in the study report. A vehicle control group of guinea pigs (5/sex) were treated in the same way with vehicle foam. In addition, a positive control group of guinea pigs (3/sex) were treated with 1-chloro-2,4-dinitrobenzene (DNCB) in 80% ethanol. Fourteen days after the induction, all animals were challenged with occluded dermal applications of econazole nitrate 1% foam at naïve test sites, except for the positive control group, which was challenged with DNCB

(0.2% in acetone). Test sites were scored for dermal irritation at 24 and 48 hr after challenge. The positive control was valid. Econazole nitrate 1% foam did not elicit a skin sensitization response in guinea pigs under the study conditions.

3. Phototoxicity test in rabbits (Study# 0432LT28.002)

Two groups of rabbits (3/sex/group) were used in the test with one group receiving the test article and vehicle with preservative and the other receiving test article and vehicle without preservative. Each rabbit had five test sites on each side, with left side being irradiated and right side not. Sites were treated with 0.1 ml econazole nitrate 1% foam (Lot# QEN 701-1, with or without preservative), vehicle foam (with or without preservative), positive control (8-methoxypsoralen), vehicle for positive control (ethanol), or untreated. The foam composition was not described in the study report. Beginning at 15 min after application on the left side, the sites on the left side of animals were irradiated (UVA/UVB, ~208 J/cm²) for 60 min. Then the test articles were applied to the sites on the right side of animals (non-irradiated). Dermal irritation was evaluated at 24, 48, 72 and 96 hr after UV exposure. The positive control was valid. No signs of phototoxicity were observed with econazole nitrate 1% foam or foam vehicle, with or without preservative.

11 Integrated Summary and Safety Evaluation

Econazole nitrate is an azole antifungal and has broad-spectrum antifungal activities. The sponsor proposed to rely upon the Agency's finding of safety for the listed drug Spectazole[®] Cream, 1%, to support some nonclinical portions of this 505(b)(2) application. Because Spectazole[®] Cream was discontinued from marketing (not for reasons of safety or effectiveness), a generic drug product, Econazole Nitrate Cream, 1%, was used as the comparator in clinical bridging studies.

In addition to relying upon the Agency's finding of safety for the listed drug, the sponsor also 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.

In a 4-week dermal toxicity study in minipigs, topical doses of 0 (vehicle: not described), 1%, and 4% econazole nitrate foam were administered to minipigs twice daily for 4 weeks (800 mg foam per application, ~1.1 and 4.6 mg/kg/day econazole nitrate). There were no significant treatment-related effects on body weight, ophthalmology, ECG, hematology, clinical chemistry, gross pathology, or histopathology. Slight dermal irritation was noted in animals treated with 4% foam. TK analysis was not performed as drug concentrations in all plasma samples were below detection limit. The NOAEL was identified as the high dose, 4% foam applied twice daily for 4 weeks.

In a 13-week dermal toxicity study in minipigs, topical doses of 0 (untreated), 0 (vehicle: clinical formulation), 0.5%, 1%, and 2% econazole nitrate foam were administered to minipigs once daily for 13 weeks (0.5, 1, and 2 mg/kg/day econazole nitrate), followed by a 4-week recovery period. Fougera Econazole Nitrate Cream 1% was also tested in this study as a reference drug. Two low dose males were euthanized one day before the scheduled necropsy. Their moribundity was not considered test article-related. There were no significant treatment-related effects on body weight, ophthalmology, ECG, hematology, clinical chemistry, gross pathology, or histopathology. Very slight dermal irritation was noted in animals treated with 2% foam. The NOAEL was identified as the high dose, 2 mg/kg/day (2% foam applied once daily).

The multiples of human exposure based on BSA and/or AUC comparison between the NOAELs identified in the repeat dose minipig studies and the maximum clinical dose are shown in the following table.

Toxicity study	Route	NOAEL (mg/kg/day)	Human equivalent dose (mg/kg/day)	AUC _{0-24h} (ng•hr/ml)	Multiples of human exposure	
					BSA*	AUC**
4-week minipig study	Dermal	4.6	4.4	N/A	11	N/A
13-week minipig study	Dermal	2.0	1.9	92	5	27

*Comparing to the mean clinical topical dose in the maximum use clinical PK trial in adults, 2.39 g/day, 0.4 mg/kg/day econazole nitrate for a 60 kg individual.

**Comparing to the mean AUC_{0-12h} obtained in the maximum use clinical PK trial in adults (3.44 ng•hr/ml)

According to summary information from literature, econazole nitrate was negative in the Ames test and did not induce structural chromosome aberration in vivo. The result of in vivo micronucleus test(s) was inconclusive (either contradictory results or insufficient data). The results of in vivo aneuploidy tests were also inconclusive. Econazole nitrate is a suspected aneugen. The human risk related to inconclusive aneuploidy tests is not clear.

Carcinogenicity data are not available for econazole nitrate. The wording regarding carcinogenicity in the Spectazole[®] Cream label will also be used in the ECOZA Foam label.

Oral administration of econazole nitrate in rats has been reported to produce prolonged gestation. Econazole nitrate has not been shown to be teratogenic when administered orally to mice, rabbits or rats. Fetotoxic or embryotoxic effects were observed in Segment I oral studies with rats receiving 10 to 40 times the human dermal dose. Similar effects were observed in Segment II or Segment III studies with mice, rabbits and/or rats receiving oral doses 80 or 40 times the human dermal dose.

Following oral administration of econazole nitrate to lactating rats, econazole and/or metabolites were excreted in milk and were found in nursing pups. Also, in lactating rats receiving large oral doses (40 or 80 times the human dermal dose), there was a reduction in post-partum viability of pups and survival to weaning; however, at these high doses, maternal toxicity was present and may have been a contributing factor.

Based on the Agency's finding of safety for the listed drug Spectazole[®] Cream and the conducted nonclinical studies with econazole nitrate foam, overall there is no significant safety concern for ECOZA Foam 1%, at the proposed clinical dose.

This NDA is approvable from a pharmacology/toxicology perspective. No postmarketing requirement is recommended for this NDA.

12 Appendix/Attachments

None.

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

/s/

JIANYONG WANG
08/02/2013

BARBARA A HILL
08/02/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205175

Applicant: AmDerma Pharmaceuticals,
LLC, Bridgewater, NJ

Stamp Date:
12/26/2012

Drug Name: Econazole Nitrate Foam, 1% **NDA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		This is an electronic CTD submission.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		The requested 13-week dermal minipig study was included in the submission. The sponsor proposes to rely upon the Agency's finding of safety on Econazole Nitrate Cream, 1% (brand drug Spectazole [®] , NDA 18751, discontinued; reference listed drug Fougera [®] , ANDA 76065) to support this NDA.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		X	The multiples of maximum recommended human dose were copied from the Fougera® Econazole Nitrate Cream, 1% label. The multiples may need adjustment if the human topical dose is determined to be different from that of the listed drug.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			It is not applicable to this NDA.
11	Has the applicant addressed any abuse potential issues in the submission?			It is not applicable to this NDA.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			This NDA is not to support a Rx to OTC switch.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

Jianyong Wang 01/11/2013

 Reviewing Pharmacologist Date

Barbara Hill see sign-off date

 Team Leader/Supervisor Date

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

/s/

JIANYONG WANG
02/08/2013

BARBARA A HILL
02/08/2013