CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205175Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205-175
Priority or Standard	Standard
Submit Date(s)	December 22, 2012
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Division / Office	DDDP/ODE III
Reviewer Name(s)	Amy S. Woitach, D.O.
Review Completion Date	September 20, 2013
Established Name	Econazole Nitrate Foam, 1%
(Proposed) Trade Name	Ecoza
Therapeutic Class	Antifungal
Applicant	Amderma Pharmaceuticals
Formulation(s)	Topical Foam
Dosing Regimen	Once daily for 4 weeks
Indication(s)	Interdigital tinea pedis
Intended Population(s)	Ages 12 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that NDA 205-175, a 505 (b)(2) application for Econazole Nitrate Foam 1% be approved for 4 week, once-daily, topical treatment of interdigital tinea pedis caused by the organisms *Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum* in patients 12 years or older.

1.2 Risk Benefit Assessment

This clinical review has 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.

Two similarly designed, randomized, double-blind, vehicle-controlled trials (302 and 303) were conducted in the US and the Dominican Republic. Study 303 differed from Study 302 in that it also included econazole cream and vehicle cream arms. The primary endpoint of "Complete Cure" at day 43 (2 weeks post-treatment) (scores of 0 [none] on all signs and symptoms, negative KOH, and negative culture) and secondary endpoints were agreed upon with the Agency under a special protocol assessment (SPA). The studies were conducted as specified in the SPA agreements.

A total of 625 subjects were randomized in 32 investigational centers. Each trial reached statistical significance in its primary endpoint. Treatment effects were generally consistent across subgroups and centers. The conclusions were consistent across various assumptions regarding missing data.

The data base for Econazole Nitrate Foam, 1% 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 Study 303). 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%.

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.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing REMS is recommended, as labeling is adequate to inform prescribers.
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1.4 Recommendations for Postmarket Requirements and Commitments

Adverse reactions regarding a drug interaction with warfarin have been identified during post approval use of Econazole Nitrate Cream. The patient population in these reports was primarily elderly. Many of the cases reported a manner of use which would likely increase systemic absorption of the econazole nitrate such as use under occlusion, genital application, and application to a large area of body surface. The majority of cases reported time to onset occurred within 23 days of econazole initiation. Many cases did not report confounding endogenous or exogenous factors known to influence response of the patient to anticoagulation. Several reports indicate that anticoagulation status had been stable for periods of one to six years prior to initiation of econazole nitrate cream.

The Agency OSE/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. The innovator label, Spectazole Cream (1982) does not include drug interaction information. The owner of Spectazole has been requested to add similar labeling in order to support the addition of potential drug-interaction to multiple generic labels.

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 based on biological plausibility. The review team does not find the potential for this interaction to be an approvability issue for this product nor does it need to be elevated to the warnings and precautions section of labeling.

Since no studies have been conducted to evaluate the drug interaction potential of econazole, the review team concurs with the clinical pharmacology review and recommends that this applicant should be requested to assess in vitro drug interaction potential as post marketing requirements (PMR's). 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.

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.

2 Introduction and Regulatory Background

Tinea pedis is 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).

The most common dermatophyteassociated with tinea pedis is *Trichophytonrubrum*. Other commonly associated dermatophytes include *E. floccosum and T. mentagrophytes* and occasionally *T. tonsurans.* These organisms are aerobic fungi that produce keratinase which breaks down cells in the stratum corneum of the skin,

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.

Econazole nitrate is a topical azole antifungal agent that is currently indicated for a variety of fungal diseases, including tinea pedis, tinea cruris, tinea corporis, and cutaneous candidiasis, as well as for the treatment of tinea versicolor. It has been marketed in the United States for more than thirty years as a cream formulation. The moiety was first approved as Spectazole (econazole nitrate) Cream 1%, (NDA 18751) on 12/23/1982. Currently, there are at least 4 generic econazole nitrate 1% creams that have been approved and marketed in the US including Fougera Econazole Nitrate Cream 1% (ANDA 76075) approved on 11/26/2002. Spectazole Cream 1 % was discontinued by Ortho Jannsen, not for reasons of safety or effectiveness. Fougera's Econazole Nitrate Cream 1% is the current RLD, as published in the current electronic version of the Approved Drug Products with Therapeutic Equivalence, commonly known as the Orange Book .

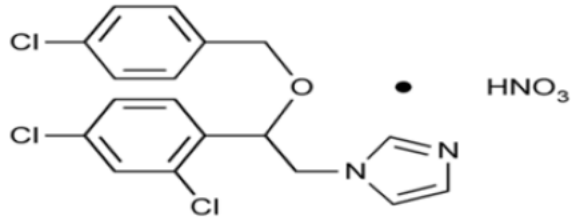
The applicant proposes to rely upon the Agency's finding of safety for Spectazole Cream (econazole nitrate), 1% to support this NDA. To support the establishment of a clinical bridge, the applicant included Fougera's Econazole Nitrate Cream 1% as a comparator in two Phase 2 PK studies (D79-2902-07 and 079-2951-109) as well as in Phase 3 study 079-2951-303. With respect to toxicology data, the applicant does not own or have rights to any of the single-dose toxicity, genetic toxicity, or reproductive toxicity data and relied on the package insert for the listed drug and available literature.

The product used as a comparator in this application's clinical trials was approved as ANDA 76075, Econazole nitrate cream 1%, on 11/26/2002, with Fougera as the sponsor. Currently, there are at least 4 generic econazole nitrate 1% creams that have been approved and marketed in the US.

The applicant, AmDerma Pharmaceuticals, LLC, submitted this 505 (b)(2) application for Econazole Nitrate Foam, 1% for the proposed indication of interdigital tinea pedis [redacted] (b) (4)

2.1 Product Information

Econazole nitrate is an antifungal agent with the chemical name (±)-1-[2,4-Dichloro-β-[(p-chlorobenzyl)oxy]phenethyl]-imidazole mononitrate. It belongs to imidazole class of antifungal agents. The molecular formula is C18H15Cl3N2O.HNO3 with a molecular weight of 444.70 g/mol and the structural formula is:



Econazole nitrate foam 1% is a white to off-white foam packaged in pressurized aerosol cans. The composition of Econazole Foam, 1% is presented below:

Ingredients	% w/w	Function
Econazole nitrate (USP)	1.00	Active
Purified water (USP)	[redacted] (b) (4)	

Stearic acid (NF)	[redacted] (b) (4)
Povidone [redacted] (b) (4) (USP)	
Propylene glycol (USP)	
Glycerin [redacted] (b) (4) (USP)	
Dimethicone [redacted] (b) (4) (NF)	
Trolamine [redacted] (b) (4) (NF)	
Polysorbate 20 (NF)	

2.2 Tables of Currently Available Treatments for Tinea Pedis

Table 1: Currently Approved Topical Antifungal Cream Formulations for Treatment of Tinea Pedis

Topical Antifungal Agents (Tinea Pedis)	NDA	Dosage (Tinea Pedis)	Dosage (Tinea Corporis/Cruris)	Date of Approval	INDICATIONS AND USAGE (LABEL)
Econazole (Spectazole)	NDA 018-751	QD for 4 weeks	QD for 2 weeks	December 23, 1982	Spectazole Cream is indicated for the topical application in the treatment of tinea pedis, tiena cruris, and tinea corporis caused by *Tichophyton rubrum, Trichophyton mentagrophytes, Tricophyton tonsurans, Microsporum canis, Microsporum audouini, Microsporum gypseum,* and *Epidermophyton floccosum,* in the treatment of cutaneous candidiasis, and in the treatment of tinea versicolor (2001).
Ciclopirox (Loprox)	NDA 018-748	BID 4 weeks	NA	December 30, 1982	Loprox Cream is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, and Microsporum canis*, candidiasis (moniliasis) due to *Candida albicans*, and tinea (pityriasis) versicolor due to *Malassezia furfur (2003)*.
Sulconazole (Exelderm)	NDA 018-737	BID 4 weeks	QD or BID for 3 weeks	August 30, 1985	EXELDERM (sulconazole nitrate) CREAM, 1.0% is an antifungal agent indicated for the treatment of tinea pedis (athlete's foot), tinea cruris, and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum*, and *Microsporum canis*, and for the treatment of tinea versicolor (2003).
Oxiconazole (Oxistat)	NDA 019-828	QD or BID 1 month	QD or BID for 2 weeks	December 30, 1988	OXISTAT Cream and Lotion are indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum*. OXISTAT Cream is indicated for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur* (2004)
(OTC) Clotrimazole (Lotrimin AF)	NDA 020-888	BID 4 weeks	BID 2-4 weeks	October 27, 1989	LOTRIMIN AF CREAM cures athelet's foot (tinea pedis), jock itch (tinea cruris) and ringworm (tinea corporis). For effective relief of the itching, cracking, burning and discomfort which can accompany these conditions (2001)
(OTC) Terbinafine (Lamisil Cream)	NDA 020-192	BID 1-2 weeks	QD 1 week	March 9, 1999	Uses: cures most athlete's foot (tinea pedis), cures most jock itch (tinea cruris) and ringworm (tinea corporis), relieves itching, burning, cracking, and scaling which accompany these conditions (2007)

Butenafine (Mentax)	NDA 020-524	Once daily for 4 weeks	combined label	October 18, 1996	Mentax® (butenafine HCl cream), 1%, is indicated for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to *M. furfur* (formerly *P. orbiculare*), interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch) due to *E. floccosum, T. mentagrophytes, T. Rubrum, and T tonsurans* (2002).
Butenafine (Mentax)	NDA 020-663	combined label	Once daily for two weeks	December 31, 1996	Mentax® (butenafine HCl cream), 1%, is indicated for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to *M. furfur* (formerly *P. orbiculare*), interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch) due to *E. floccosum, T. mentagrophytes, T. Rubrum, and T tonsurans* (2002).
(OTC) Butenafine (Lotrimin Ultra)	NDA 021-307	BID 1 week	QD 2 weeks	December 7, 2001	Uses: cures most athlete's foot between the toes, jock itch and ringworm. Revlieves itching, burning, cracking, and scaling which accompany these conditions (2001)
Sertaconazole (Ertaczo)	NDA 021-385	BID 4 weeks	No indication for tinea corporis or cruris	December 10, 2003	ERTACZO (sertaconazole nitrate) Cream, 2%, is indicated for the treatment of interdigital tinea pedis in immunocompetent patients 12 years of age an older, caused by: *Trichophyton rubrum, Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.
Ketoconazole (Generic)	ANDA 075-581 and 076-294	QD 6 weeks	QD 2 weeks	75-581: April 25, 2000 76-294: April 28, 2004	Ketoconazole Cream 2% is indicated for the topical treatment of tinea corporis, tinea cruris and tinea pedis caused by Trichophyton rubrum, T. mentagrophytes and Epidermophyton floccsum; in the treatment of tinea (pityriasis) versicolog caused by Malassezia furfur (Pityrosporum orbiculare); in the treatment of cutaneous candidasis caused by Candida spp. and in the treatment of seborrheic dermatitis (2002).
Naftifine (Naftin)	NDA 019-599	QD for 2 weeks	QD for 2 weeks	January 13, 2012	NAFTIN Cream, 2% is an allylamine antifungal indicated for the treatment of interdigital tinea pedis, tinea, cruris, and tinea coporis caused by the organism *Trichophyton rubrum* in adults ≥ 18 years of age.
Nafitine (Naftin) Gel	**NDA 204-286**	**QD for 2 weeks**	**NA**	**June 27, 2013**	**NAFTIN (naftifine hydrochloride) Gel, 2% is an allylamine antifungal indicated for the treatment of interdigital tinea pedis caused by the organisms Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum in patients 18 years of age and older.**
Lotrisone 1% cream; lotion	**NDA 18827; 20010**	**BID for 4 weeks**	**BID for 2 weeks**	**July 10, 1984; December 8, 2000**	**LOTRISONE Cream and Lotion are indicated in patients 17 years and older for the topical treatment of symptomatic inflammatory tinea pedis, tinea cruris, and tinea corporis due to Epidermophyton floccosum, Trichophyton mentagrophytes, and Trichophyton rubrum. Effective treatment without the risks associated with topical corticosteroid use may be obtained using a topical antifungal agent that does not contain a corticosteroid, especially for noninflammatory tinea infections. The efficacy of LOTRISONE Cream or Lotion for the treatment of infections caused by zoophilic dermatophytes (eg, Microsporum canis) has not been established. Several cases of treatment failure of LOTRISONE Cream in the treatment of infections caused by Microsporum canis have been reported.**

Source: Internal DDDP database and FDA approved labeling

2.3 Availability of Proposed Active Ingredient in the United States

Approved products with Econazole Nitrate as an active ingredient are:

- Econazole Nitrate Cream 1% 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,* in the treatment of cutaneous candidiasis, and in the treatment of tinea versicolor (approved December 23, 1982 and currently marketed as a generic).

Econazole Nitrate is also available outside the US as the active ingredient in topical cream and vaginal ovules (Gyno-Pevaryl) for vulvovaginal mycoses and mycotic balanitis

2.4 Important Safety Issues With Consideration to Related Drugs

Econazole nitrate is an imdiazole antifungal that is administered topically. Hepatic dysfunction can develop when azoles are given orally, particularly with ketoconazole. Voriconazole is associated with a number of adverse effects in humans, including vision disturbances.

Other imidazoles include Clotrimazole 1% (Lotrimin, Mycelex, OTC), Miconazole nitrate 2% (Monistat-Derm, Micatin, OTC),Ketoconazole 2% (Nizoral),Oxiconazole nitrate 1% (Oxistat) and Sulconazole (Exelderm) which are administered topically and are marketed both by prescription and over-the-counter. Topically administered imidazole antifungal products, including econazole nitrate cream are regarded as generally safe. Local skin reactions (erythema, stinging, burning and itching) have been reported.

Because warfarin is also metabolized via the cytochrome P450 system, it is well-established that orally administered azole antifungals may increase warfarin's serum concentration. It has been assumed that the systemic absorption of topical antifungals would not be sufficient to influence warfarin's metabolism. However, concomitant administration of miconazole and warfarin has resulted in enhancement of anticoagulant effect. Similar cases have been reported with the use of topical econazole cream, as discussed later in this review. Cases of bleeding and bruising following the concomitant use of warfarin and topical, intravaginal, or oral miconazole have been reported.

There were no cases of hepatic dysfunction, visual disturbances, bruising or bleeding identified in the phase 3 studies for Econazole Nitrate Foam, 1% .

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The IND for Econazole Nitrate Foam, 1% 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).

SPA Agreement (2): January 7, 2010
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.

- proposed primary endpoint of "the proportion of subjects with complete cure at Day 43, defined as a negative KOH, negative culture and no evidence of clinical disease as indicated by scores of 0 for each sign or symptom (erythema, scaling, fissuring, maceration, vesiculation, and pruritus)" is acceptable
- proposal to use LOCF as the primary method of imputing missing data along with three sensitivity analyses using alternate imputation strategies is acceptable
- proposal to control the error rate for the secondary endpoints using a sequential, step-down method is acceptable
- proposed time points for collection of fungal cultures are acceptable
- For study 303 we reiterate our recommendation that a small cream arm be added to maintain blinding

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 and conducted a pediatric PK trial evaluating subjects aged 12-17 years.

2.6 Other Relevant Background Information

Protocols 079-2951-302 and 079-2951-303 were amended after SPA agreements were reached. The modifications to the protocols were minor and did not impact the SPA agreements. The amendments are discussed in section 5.3.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission was acceptable. 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 the Division of Scientific Integrity (DSI) inspection for this application. The study results did not show huge differences in study center enrollments or treatment effect and there is not a substantial change in indication or the inclusion of a new, potentially vulnerable population to warrant an inspection.

Investigator sites for studies 302 and 303 are listed in the tables below.

Table 2: Table of Investigators (study 302)

Investigational Site Number	Principal Investigator	Investigational Site Name/City, State
01	Jeffrey Adelglass, MD	Research Across America Plano, TX 75093
02	Boni Elewski, MD	UAB Dermatology Birmingham, AL 35249
03	Alan Fleisher, MD	Dept. of Dermatology Wake Forest University Health Sciences Winston-Salem, NC 27157
04	Michael H. Gold, MD	Tennessee Clinical Research Center Nashville, TN 37215
05	Robert S. Haber, MD	Haber Dermatology South Euclid, OH 44118
06	Mark Ling, MD, PhD	MedaPhase, Inc. Newnan, GA 30263
08	Jennie Muglia, MD	Rhode Island Hospital Providence, RI 02903
09	Francisco Flores, MD	FXM Research Miramar Miramar, FL 33027
10	Cyaandi Dove, DPM	Advanced Foot & Ankle Center, Inc. Las Vegas, NV 89119
11	Cynthia Strout, MD	Coastal Carolina Research Center Mt. Pleasant, SC 29464
12	Daniel M. Stewart, DO	Michigan Center for Research Corp DBA Skin Care Research Clinton Township, MI 48038

13	Daisy Margarita Blanco Falette, MD	Instituto Dermatologico/Santo Domingo, Republica Dominicana
14	Ynca Nina Vasquez, MD	Instituto Dermatologico Unidad Sur/Santo Domingo, Republica Dominicana
16	Michelle L. Look, MD	San Diego Sports Medicine & Family Health Center/San Diego, CA

Table 3: Table of Investigators (study 303)

Investigational Site Number	Principal Investigator	Investigational Site Name/City, State
01	William Abramovits, MD	Dermatology Treatment and Research Center/Dallas, TX
02	Sunil S. Dhawan, MD	Center for Dermatology Clinical Research, Inc./Fremont, CA
03	Michael Jarratt, MD	DermResearch, Inc./Austin, TX
04	Terry M. Jones, MD	J&S Studies, Inc./ College Station, TX
05	Robert J. Kaylor, DPM	Deaconess Clinic Downtown Research Institute, Inc./ Evansville, IN
06	Steven E. Kempers, MD	Minnesota Clinical Study Center/Fridley, MN
07	Alicia Barba, MD	International Dermatology Research, Inc./Miami, FL
08	David M. Pariser, MD	Virginia Clinical Research, Inc./Norfolk, VA
09	Edward J. Primka III, MD	Dermatology Associates of Knoxville, PC/Knoxville, TN
10	Phoebe Rich, MD	Oregon Dermatology and Research Center/Portland, OR
11 [a]	Jonathan Kantor, MD	North Florida Dermatology Associates, PA/Jacksonville, FL 32204
12	Joel Schlessinger, MD	Advanced Skin Research Center/Skin Specialists, PC/Omaha, NE
13	Harry Sharata, MD	Madison Skin & Research, Inc./Madison, WI
14	Teresa S. Sligh, MD	Providence Clinical Research/Burbank, CA
15	Marta I. Rendon, MD	Skin Care Research, Inc./Boca Raton, FL
19	Howard Sofen, MD	Dermatology Research Associates/Los Angeles, CA

20	Oscar De Valle, MD	West Houston Clinical Research Service (WHCRS)/Houston, TX
21	David A. Rodriguez, MD	Dermatology Associates and Research/Coral Gables, FL
22	Walter K. Nahm, MD, PhD	University Clinical Trials, Inc./San Diego, CA
[a] Investigational Site 11 screened subjects, but none were enrolled.		

3.2 Compliance with Good Clinical Practices

The studies were conducted in compliance with good clinical practices.

The applicant affirmed that the studies were conducted in compliance with the principles of the Declaration of Helsinki, the current Good Clinical Practice (GCP) guidelines, and other applicable regulations. The investigator and all investigational site staff conducted the study in compliance with the protocol. The protocol, informed consent/assent documents, recruitment advertisements, and any amendments to these items had IRB approval prior to study initiation. Voluntary informed consent/assent was given by every subject prior to the initiation of any study related procedures.

3.3 Financial Disclosures

Financial disclosure was complete. Financial disclosure forms were reviewed, there were no reported financial conflict of interest was for an investigator participating in the phase 3 studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No critical issues were identified during the review cycle by the CMC reviewer, Dr. Nina Ni. 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. CMC has concluded that the NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. However, CMC has also concluded that this NDA is ***not*** ready for approval in its present form as of the date of this review until labeling is satisfactorily resolved.

Issues raised during the review period included discussion regarding a process impurity with potential genotoxicity. The applicant proposed to set the specification (b) (4) at NMT (not more than) (b) (4) in the drug substance. To determine if this is acceptable Dr. Jianyong Wang reviewed toxicity data regarding this substance. (b) (4) The daily topical exposure to this impurity would be less than (b) (4) when controlled at NMT (b) (4) in the drug substance (b) (4) which is much lower than the acceptable qualification threshold of 1.5 µg for genotoxic and carcinogenic impurities. Therefore, there is no significant safety concern for this impurity when controlled at NMT (b) (4) in the drug substance.

Issues related to solubility of the drug product (b) (4) were successfully resolved following informational requests with the applicant. CMC did not agree with the applicant's conclusion (b) (4)

(b) (4)

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

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

An IVRT study was conducted to bridge site change from (b) (4) to (b) (4) the U.S. and process changes. The in vitro release testing (IVRT) method and its validation was reviewed and found adequate by Dr. Kelly Kitchens.

Currently, ONDQA, under a new initiative, has been recommending the use of modifier "topical" to the dermatologic foam products. The recommended established name for this product is econazole nitrate topical foam. From a clinical perspective, this reviewer has no objective the proposed established name.

4.2 Clinical Microbiology

No critical issues were identified during the review cycle by the clinical microbiology reviewer, Dr. Shukal Bala. Overall, the results of the three clinical trials show Econazole Nitrate Foam, 1% to be effective in improving clinical and mycological cure rates compared to the vehicle group; the cure rates were comparable to the referenced drug, econazole nitrate cream.

T. rubrum was the most common dermatophyte isolated. Econazole Nitrate Foam, 1% was effective in patients with infections due to *T. rubrum*, *T. mentagrophytes*, and *E.floccosum*; MICs of all baseline isolates were ≤0.5 µg/mL with a MIC90 of ≤0.016 µg/mL. There was no correlation between MICs of baseline isolates and clinical or mycological response. There does not appear to be any change in MIC values of isolates collected after treatment compared to the baseline isolates.

The applicant proposes to label Econazole Nitrate 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. It is this reviewer's recommendation that labeling should reflect the organisms commonly associated with the indication and in which at least some subjects have been evaluated.

4.3 Preclinical Pharmacology/Toxicology

The applicant 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 applicant 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 Foam, 1% did not induce dermal irritation in rabbits. No skin sensitization or phototoxicity was noted for Econazole Nitrate Foam, 1% , 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. 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.

Dr. Jianyong Wang, pharmacology/ toxicology reviewer has concluded that 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.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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.

4.4.2 Pharmacodynamics

The pharmacodynamics of Econazole Nitrate Foam, 1% have not been established.

4.4.3 Pharmacokinetics

The applicant conducted PK assessment in the following trials:

- 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

In the adult trial, 19 subjects (male and female) with tinea pedis applied Econazole Nitrate Foam, 1% once daily for 29 days. Subjects applied a mean daily amount of2.4 g of econazole nitrate foam 1% to soles, toes, interdigital spaces and tops of both feet up to the ankles. Blood samples were obtained on Day 29 at pre-dose and 1, 2, 4, 6, 8, and 12 hours after application. Results (mean ± SD) showed the time to reach peak plasma concentrations (Tmax) was 6.8 ± 5.1 h with maximum concentration (Cmax) of 417 ±218 pg/ml. The area under the concentration time curve for the first 12 hours post application on Day 29 (AUC(0-12)) was 3440 ± 1920 pg-h/ml.

In the pediatric trial study, 18 subjects (male and female ages 12 - 17) with interdigital tinea pedis and positive fungal cultures were treated with Econazole Nitrate Foam, 1% once daily for 4 weeks. Subjects applied a mean daily amount of 3.2 g of Econazole Nitrate Foam, 1% to soles, toes, interdigital spaces and tops of both feet up to the ankles. Blood samples were obtained on Day 28 at pre-dose and 7 h and 11 h post-dose. The mean ± SD econazole plasma concentration was 397 ± 289, 534 ± 745 and 575 ± 638 pg/mL at pre-dose and 7 h and 11 h post-dose, respectively.

Dr. Chinmay Shukla concluded 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. 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.

The review team has found that this slight increase in systemic bioavailability is acceptable since the intended labeled use of this product is for tinea pedis, a disease with limited body surface area and no safety signal has been detected in the clinical studies. Also, given the long history of econazole use and the lack of QT related adverse events reported, the team finds that granting a waiver for conducting TQT assessment appears reasonable.

The clinical pharmacology review team is recommending that this applicant should be requested to assess in vitro drug interaction potential with Coumadin as post marketing requirements (PMR's). 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. Based on the in vitro results, the need for further in vivo assessments and appropriateness for labeling will be evaluated at that time. A more detailed discussion regarding this PMR is provided in section 1.4.

Comment: While this reviewer has no objection to the clinical pharmacology team's recommendation for in-vitro drug interaction assessment. The clinical/ regulatory implications of the study outcome are not fully obvious. If inhibition/ induction of the enzymes occur at a concentration below the systemic level expected from clinical use, in vivo assessment or additional labeling may be warranted. If inhibition/ induction of the enzymes occur at a concentration above the systemic level expected from clinical use, it is not clear to this reviewer how the labeling describing post-marketing cases would be affected. In vitro data may need to be added to labeling.

Dr. Shukla's conclusion is that from a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed , and the post marketing DDI assessments are agreed to by the applicant.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The data reviewed were from trials conducted by the sponsor. There are total of 8 trials: 2 pivotal trials (079-2951-302 and 079-2951-303), 2 pharmacokinetic trials (D79-2902-07; 079-2951-109), and four dermal safety trials (079-2951-104; 079-2951-105; 079-2951-106; 079-2951-107). See Table 4 for a listing and summary of these trials.

Table 4: Summary of Clinical Trials

Protocol	Study Objective(s)	Study Design	Subject Population (Plan/Actual)	Number of Sites (Location)	Treatment Group(s) (No. Subjects Randomized)	Dosing Regimen/ Duration of Treatment	Primary Endpoint	Study Period
079-2951-104 (Phase 1) 21 Day Irr.	• To determine skin irritation potential of Econazole Nitrate Foam, 1% and Foam Vehicle • To determine the safety of Econazole Nitrate Foam, 1% and Foam Vehicle	Randomized, single-center, vehicle-controlled, within-subject study	Healthy subjects of age ≥ 18 years (30/37)	1 (US)	• Econazole Nitrate Foam, 1% (37) • Foam Vehicle (37) • 0.2% SLS (positive control) (37) • 0.9% saline (negative control) (37)	21 topical Applications/ 3 weeks	Mean cumulative irritation score	28 Dec 2011 to 25 Jan 2012
079-2951-105 (Phase 1) RIPT	• To determine the sensitization potential of Econazole Nitrate Foam, 1% and Foam Vehicle • To determine the safety of Econazole Nitrate Foam, 1% and Foam Vehicle	Randomized, single-center, vehicle-controlled, within-subject study	Healthy subjects of age ≥ 18 years (200/250)	1 (US)	• Econazole Nitrate Foam, 1% (250) • Foam Vehicle (250) • 0.1% SLS (positive control) (250) • 0.9% saline (negative control) (250)	10 topical Applications/ 6-8 weeks	Mean dermal response score	09 Jan 2012 to 25 Feb 2012
079-2951-106 (Phase 1) Phototox.	• To determine skin irritation potential of Econazole Nitrate Foam,	Randomized, single-center, vehicle-controlled, within-subject	Healthy subjects of age ≥ 18 years (30/33)	1 (US)	• Econazole Nitrate Foam, 1% (33) • Foam Vehicle	1 topical application over a 4-day period	Mean numerical equivalent score (site assessment	29 Dec 2011 to 10 Feb 2012

	1% and Foam Vehicle followed by UV exposure • To determine the safety of Econazole Nitrate Foam, 1% and Foam Vehicle	study			(33) • 1 untreated, irradiated control site per subject		score of erythema and edema)	
079-2951-107 (Phase 1) Photoallergy	• To determine the photo-sensitization potential of Econazole Nitrate Foam, 1% and Foam Vehicle • To determine the safety of Econazole Nitrate Foam, 1% and Foam Vehicle	Randomized, single-center, vehicle-controlled, within-subject study	Healthy subjects of age ≥ 18 years (50/59)	1 (US)	• Econazole Nitrate Foam, 1% (59) • Foam Vehicle (59) • 1 untreated, Irradiated control site per subject	7 topical Applications/ 6 weeks	Mean numerical equivalent score (dermal response scores) postirradiation	28 Dec 2011 to 24 Feb 2012
D79-2902-07 (Phase 2)	• To substantiate a clinical bridge Between Econazole Nitrate Foam, 1% and Econazole Nitrate Cream 1% based upon clinical outcome, safety, and plasma pharmacokinetic (PK) data • To determine and compare the safety, including local tolerability, and efficacy of Econazole Nitrate Foam, 1% with Econazole Nitrate Cream 1% and the Foam Vehicle	multi-center, evaluator-blinded, randomized, vehicle-controlled, parallel-group study	Healthy subjects of age ≥ 18 years with a clinical diagnosis of interdigital and/or moccasin-type tinea pedis (120/135)	6 (US)	• Econazole Nitrate Foam, 1% (43) • Foam Vehicle (47) • Econazole Nitrate Cream 1% (45)	1 daily application/ 4 weeks	Complete cure at Day 43	27 Mar 2008 to 25 Sept2008
079-2951-109 (Phase 2) Ped PK	To compare the steady state PK of Econazole Nitrate Foam, 1% with Econazole	Multi-center, randomized, double-blind, reference listed drug-controlled, parallel-group	Male and female subjects aged ≥ 12 to < 18 years with a clinical diagnosis of	8 (7 US; 1 Central America)	• Econazole Nitrate Foam, 1% (25) • Econazole NitrateCream 1% (25)	A thin uniform coat applied once daily to the soles, toes, interdigital	Plasma Econazole nitrate concentrations	21 Sept2011 to 30 Apr 2012

	Nitrate 1% Cream in subjects with interdigital tinea pedis aged 12 years to less than 18 years who were maximally treated.	study	interdigital tinea pedis (42/50)	(2 US without enrollment)		spaces, and the tops of both feet (up to the ankles) for 4 weeks		
079-2951-302 (Phase 3)	To determine and compare the safety and efficacy of Econazole Nitrate Foam, 1% and Foam Vehicle in subjects with interdigital tinea pedis	Randomized, double-blind, parallel-group, vehicle-controlled multi-center study	Male and female subjects aged ≥ 12 years with a clinical diagnosis of interdigital tinea pedis (224/267)	16 (14 US; 2 Central America) (2 without enrollment)	• Econazole Nitrate Foam, 1% (132) • Foam Vehicle (135)	A thin uniform coat applied once daily to all clinically affected interdigital regions of both feet for 4 weeks	Complete cure at two weeks post-treatment [Day 43]	24 May 2011 to 12 Apr 2012
079-2951-303 (Phase 3)	To determine and compare the safety and efficacy of Econazole Nitrate Foam, 1% and Foam Vehicle in subjects with interdigital tinea pedis. Econazole Nitrate Cream 1% was included as an evaluator-blinded comparator for safety purposes only to support a clinical bridge between Econazole Nitrate Foam, 1% and Econazole Nitrate Cream 1%; Placebo Cream was included for Blinding purposes only.	Randomized, double-blind, parallel-group, vehicle-controlled multi-center study	Male and female subjects aged ≥ 12 years with a clinical diagnosis of interdigital tinea pedis (336/358)	22 (US) (2 without enrolment)	• Econazole Nitrate Foam, 1% (119) • Foam Vehicle (119) • Econazole Nitrate Cream 1% (80) • Placebo Cream (40)	A thin uniform coat applied once daily to all clinically affected interdigital regions of both feet / 4 weeks	Complete cure at two weeks post-treatment [Day 43]	02 Jun 2011 to 04 Apr 2012

Source: Sponsor's 5.3.5.3 Integrated Summary of Safety Table 1

5.2 Review Strategy

A brief summary of the protocol for pivotal trials will be presented is this section. The protocols were previously reviewed under Special Protocol Assessment.
Efficacy evaluation regarding this NDA is presented in section 6 Review of Efficacy. Efficacy analysis is based on modified intent-to-treat (MITT) population. Safety evaluation regarding this NDA is presented in section 7 Review of Safety. The safety data analysis is based on safety population defined as a subset of all subjects who received study drug at least once. The review includes all of the safety data from the pivotal and pharmacokinetic trials. Additional safety from the four provocative dermal safety trials is reviewed in section 7.4.5 Special Safety Studies/Clinical Trials.

Review of the pharmacokinetic data was deferred to Clinical Pharmacology. Key review points and their clinical implications are presented in section 7.2.5 Metabolic, Clearance, and Interaction Workup.

5.3 Discussion of Individual Studies/Clinical Trials

Similarly designed protocols 079-2951-302 and 079-2951-303 were submitted under IND 77,523. Study 303 differed from Study 302 in that it also included econazole cream and vehicle cream arms Also, photographic assessments were included in a subset of subjects in study 302 and ECG assessment was included in a subset of subjects in study 303. The protocols were amended after SPA agreements were reached. The modifications to the protocols were minor and did not impact the SPA agreements. The major changes are provided in the table below.

Table 5: Trial 302 protocol amendments

Amendment	Date	Major Changes
1	January 19, 2011	Photography at baseline and end of study added to schedule of assessments at 2 investigational sites
		AE reporting requirements updated
2	August 23, 2011	Subject numbering clarified
		Dosing instructions clarified
		Procedure for discontinuation due to negative baseline fungal culture clarified
3	October13, 2011	Increased number of investigational sites to 16 (within and outside US)

Table 6: Trial 303 protocol amendments

Amendment	Date	Major Changes
1	19 January 2011	Photographic assessments removed

		AE reporting requirements updated
2	23 August 23 2011	Clarifications to subject numbering, study drug administration, and early termination due to negative baseline fungal culture

Trial 302 was conducted from 24 May 2011 to 12 April 2012 at 16 sites in the US (14) and Dominican Republic (2); trial 303 was conducted from 02 June 2011 to 04 April 2012 at 21 sites in the US.

Trial design

Protocol 079-2951-302, is a multi-center, randomized, double blind, vehicle-controlled, 2-arm study (Econazole Nitrate Foam, 1% vs. vehicle). Intended enrollment was for 224 subjects aged 12 years and older (randomized 1:1) presenting with a clinical diagnosis of interdigital tinea pedis and a positive KOH finding at the Screening/Baseline visit. The expectation was for 67% subject inclusion in the MITT population (based on confirmed dermatophyte infection) which would result in approximately 150 subjects (75 per arm) in the MITT population.

The assigned study medication was to be applied once daily preferably in the mornings for 4 weeks. Subjects were to be evaluated at baseline, Day 8, Day 15, Day 29, and Day 43. Efficacy was to be assessed at Day 43 (Week 6) clinically and with repeat mycological cultures/KOH.

Protocol 079-2951-303, is a multi-center, randomized, double blind, vehicle-controlled, 4-arm study (Econazole Nitrate Foam, 1% vs. vehicle vs. econazole nitrate cream vs. vehicle). Intended enrollment was for 336 subjects (randomized 3:3:2:1) aged 12 years and above presenting with a clinical diagnosis of interdigital tinea pedis and a positive KOH finding at the Screening/Baseline visit .The expectation was for 67% subject inclusion in the MITT population (based on confirmed dermatophyte infection) which would result in approximately 225 subjects (75 per Econazole Nitrate Foam 1% and the Foam Vehicle treatment arms, 50 in the Econazole Nitrate Cream 1%, and 25 in the Placebo Cream)in the MITT population.

The assigned study medication will be applied once daily preferably in the mornings for 4 weeks. Subjects will be evaluated at baseline, Day 8, Day 15, Day 29, and Day 43. Efficacy will be assessed at Day 43 (Week 6) clinically and with repeat mycological cultures/KOH.

For both protocols:

Subjects with negative baseline dermatophyte cultures were discontinued. Subjects who missed the Day 8 visit but were found to have a negative baseline culture result were to be contacted and instructed to discontinue dosing and scheduled to return to the clinic to be discontinued; if cultures were pending at Day 8, the subjects continued treatment until the next visit. Repeat cultures and KOH analyses were conducted at Visits 4 and 5 (end of treatment and end of study visits, respectively). Safety evaluation and clinical grading were performed at all visits. Fasting end of treatment laboratory tests (chemistry, hematology and urinalysis) were performed on blood samples collected at Day 29. Subjects with clinically significant laboratory abnormalities at the end of treatment visit as assessed by the investigator were to have the laboratory tests repeated at Day 43 (end of study). Digital electrocardiograms (ECGs) were to be performed at screening/baseline, Day 29 and Day 43 for all subjects at 4 selected investigational sites (approximately 126 subjects). Blood samples were to be obtained at baseline and Days 29 and 43 for all subjects who underwent an ECG; the blood samples may have been analyzed for econazole nitrate levels if there were significant ECG changes noted at Days 29 and 43.

Major inclusion criteria

1. Be at least 12 years of age and of either sex
2. Have a clinical diagnosis of interdigital tinea pedis involving at least 2 web spaces in total which extends no more than approximately 1 inch proximal to the web spaces or metotarsophalangeal joints with at least i) moderate scaling and ii) mild erythema defined as a grade 2 and grade 1, respectively on the Grading of Signs and Symptoms at baseline.
3. Have microscopic evidence (positive KOH) of the presence of fungi. Evaluable subjects must have a positive KOH and a fungal culture positive for a dermatophyte in the skin scrapings taken at the Baseline Visit. Subjects with a positive KOH may be entered into the study pending the results of the fungal culture.
4. Be in good health and free of any disease or physical condition which might in the Investigator's opinion, expose the subject to an unacceptable risk by study participation.
7. Females must be non-pregnant (confirmed by a negative urine pregnancy test at baseline, non-lactating and not intending to become pregnant during the course of the study.

Major exclusion criteria

1. Is pregnant, nursing, or planning a pregnancy during the study.
2. Has used topical antifungals or topical corticosteroids on the feet within 30 days prior to the start of the study.
3. Has received systemic antifungal therapy within 12 weeks prior to the start of the study medication.
4. Has used systemic antibacterials or systemic corticosteroids within 30 days prior to the start of the study. Systemic corticosteroids do not include intranasal, inhaled, and ophthalmic corticosteroids used for the management of allergies, pulmonary disorders, or other conditions.

5. Has a history of uncontrolled diabetes mellitus or is immunocompromised (due to disease e.g. HIV or medications)
6. Has concurrent tinea infection e.g. tinea versicolor, tinea cruris, moccasin-type tinea pedis, etc. (in the opinion of the Investigator).
7. Onychomycosis involving > 20% of the area of either great toenail or involvement of more than five toenails in total.
8. Has any other skin disease which might interfere with the evaluation of tinea pedis.

Treatment
The assigned study medication will be applied once daily preferably in the mornings for 4 weeks.

Efficacy assessment
Subjects will be evaluated at baseline, Day 8, Day 15, Day 29, and Day 43. Efficacy will be assessed at Day 43 (Week 6) clinically and with repeat mycological cultures/KOH.

The primary analysis population, the MITT population, is defined as all subjects randomized and dispensed medication with positive baseline KOH and fungal cultures. The per protocol population includes MITT subjects who

(1) meet all inclusion/exclusion criteria,
(2) do not take interfering concomitant medications,
(3) attend the Day 29 and Day 43 evaluations (unless they discontinue due to a treatment related adverse event or lack of treatment effect/worsening of condition),
(4) applied 80-120% of expected doses, and
(5) had the Day 29 and 43 visits within a visit window of ±4 days.

Primary Efficacy Endpoint:
The primary efficacy endpoint is complete cure at Day 43, defined as a negative KOH, negative culture, and no evidence of clinical disease as indicated by scores of 0 (none) on each sign or symptom (erythema, scaling, fissuring, maceration, vesiculation, and pruritus). Each sign and symptom is evaluated on the following scale:

0	None	No signs or symptoms present
1	Mild	Barely abnormal
2	Moderate	Distinctly present abnormality
3	Severe	Intense involvement or marked abnormality

Secondary Efficacy Endpoints:
• Effective Treatment defined as negative KOH, negative culture, no or mild erythema and/or scaling (score of 0 or 1) with all other signs and symptoms being at Day 43.
• Mycological Cure defined as negative KOH and negative culture at Day 43.

Other Efficacy Endpoints:

Investigator and subject assessments of clinical improvement (success=good, very good, or excellent; failure=fair or poor) at Days 29 and 43, and each sign and symptom of tinea pedis at each visit.

Statistical analysis plan
The primary and secondary endpoints were analyzed with the Cochran-Mantel-Haenszel (CMH) test stratified on analysis center.

Centers that did not enroll at least 8 econazole foam and at least 8 vehicle foam subjects were pooled into analysis centers (smallest center was pooled with the largest center that did not meet the sample size requirements, etc. until all analysis centers met the sample size requirements). Consistency of treatment response across analysis centers was assessed with the Breslow-Day test.

The primary analysis population for efficacy endpoints was the MITT (all randomized subjects who were dispensed product and had positive baseline KOH and culture). The primary method of handling missing data was last observation carried forward (LOCF).The protocols specified three sensitivity analyses for missing data:

- impute all subjects with missing values as failures
- impute all subjects with missing values as successes
- impute a proportion of subjects with missing data on each arm as successes (fractions of vehicle subjects will be rounded up and fractions of econazole foam subjects will be rounded down)

Safety assessment
At all visits, a safety evaluation and clinical grading will be performed. Local and systemic adverse event information will be collected. Blood will be drawn to obtain fasting baseline and end of treatment laboratory tests (chemistry, hematology, urine pregnancy test, and urinalysis). On approximately 126 subjects enrolled at 4 selected sites, 12-lead ECG monitoring and QT/QTc assessments will be performed.
All subjects with baseline dermatophyte cultures that are negative will be included in the safety population. Laboratory analysis will be completed at time of discontinuation. Subjects will be discontinued for adverse events as determined by the investigator, worsening of condition, and pregnancy. Prior to enrolling in the study female subjects will be advised of the importance of avoiding pregnancy during trial participation and of the potential risk factors for an unintentional pregnancy. Any pregnancies which occur during the trial will be followed for outcome and the offspring will be followed for a minimum of 8 weeks

Comment: The Phase 3 protocols are appropriately designed to evaluate a new formulation of an approved topical antifungal for the indication of interdigital tinea pedis. The primary endpoint is appropriate to determine efficacy as is the secondary endpoints of effective treatment and mycological cure. These endpoints are consistent with

endpoint evaluations conducted in other applications approved for tinea pedis and were agreed to with the Agency under a SPA. The "other secondary endpoints" of investigator and subject clinical improvement scores will have no regulatory utility and were not agreed to under the SPA. Inclusion of the econazole cream arm was part of the clinical bridge to address certain elements of the nonclinical requirements and safety of the moiety in this new foam formulation.

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6 Review of Efficacy

Efficacy Summary

Two similarly designed, randomized, double-blind, vehicle-controlled trials (302 and 303) were conducted in the US and the Dominican Republic. Study 303 differed from Study 302 in that it also included econazole cream and vehicle cream arms. The primary endpoint of "Complete Cure" at day 43 (2 weeks post-treatment) (scores of 0 [none] on all signs and symptoms, negative KOH, and negative culture) and secondary endpoints were agreed upon with the Agency under a special protocol assessment (SPA). The studies were conducted as specified in the SPA agreements.

A total of 625 subjects were randomized in 32 investigational centers. Each trial reached statistical significance in its primary endpoint. Treatment effects were generally consistent across subgroups and centers. The conclusions were consistent across various assumptions regarding missing data.

6.1 Indication

The sponsor proposes that Econazole Nitrate Foam 1% receive the following indication: For the topical treatment of interdigital tinea pedis (b) (4)

As discussed below (section 6.1.7), the conclusion of this clinical review, as well as the recommendation of the review team, is that only the indication of interdigital tinea pedis in *Tichophyton rubrum, Tichophyton mentagrophytes and Epidermophyton floccosum* in ages 12 and older is supported by the applicant's clinical development program.

6.1.1 Methods

The protocol defined three analysis populations:

- MITT – all randomized subjects who were dispensed product and had positive baseline KOH and culture
- Per protocol – subset of MITT subjects who completed the Day 29 and Day 43 visits (unless discontinued for treatment-related adverse events or lack of

treatment effect), met all inclusion/exclusion criteria, did not take interfering concomitant medications, and applied 80-120% of expected doses
- Safety – all randomized subjects who had at least one application of investigational product and at least one post-baseline evaluation

The primary analysis population for efficacy endpoints was the MITT.

6.1.2 Demographics

Baseline demographics were generally balanced across the treatment groups in the two studies. The demographics were similar among the all-randomized and the MITT population. The mean age of the subjects was approximately 41 years, with approximately 2% of subjects less than 18 years of age, and 4% of subjects 65 years of age or older. The majority of subjects were male (62-75%).

Table 7: Demographics (study 302)

	Randomized			
	Econazole Foam N=132	Vehicle Foam N=135	Econazole Foam N=82	Vehicle Foam N=83
Age (years)				
Mean	41.7	42.4	40.1	41.3
Range	12-71	14-71	16-71	17-69
<18 years	4 (3%)	3 (2%)	2 (2%)	1 (1%)
18 to 64 years	123 (93%)	126 (93%)	77 (94%)	78 (94%)
65 + years	5 (4%)	6 (4%)	3 (4%)	4 (5%)
Gender				
Male	87 (66%)	79 (59%)	54 (66%)	49 (59%)
Female	45 (34%)	56 (41%)	28 (34%)	34 (41%)
Race				
White	53 (40%)	53 (39%)	32 (39%)	34 (41%)
Black or Afric.-Amer.	60 (45%)	60 (44%)	37 (45%)	37 (45%)
Other	19 (14%)	22 (16%)	13 (16%)	12 (14%)
Ethnicity				
Hispanic or Latino	65 (49%)	65 (48%)	44 (54%)	36 (44%)
Not Hispanic or Latino	67 (51%)	70 (52%)	38 (46%)	47 (57%)
Geographic Region				
United States	93 (70%)	93 (69%)	57 (70%)	64 (77%)
Dominican Republic	39 (30%)	42 (31%)	25 (30%)	19 (23%)

Source: pg 52 of study report for Study 302 and Agency statistical review.

In Study 302, 40% of subjects were white and 45% were black or African-American. Close to half of the subjects reported their ethnicity as Hispanic or Latino.

Comment: The race demographics approach those of the US population. This study has a slightly increased number of black/African-American and Hispanic/Latino subjects which is likely due to subjects enrolled in study centers in the Dominican Republic.

Table 8: Demographics (study 303)

	Randomized			
	Econazole Foam N=119	Vehicle Foam N=119	Econazole Cream N=80	Vehicle Cream N=40
Age (years)				
Mean	40.9	42.0	41.2	39.7
Range	18-80	12-71	12-89	19-71
<18 years	0 (0%)	2 (2%)	2 (3%)	0 (0%)
18 to 64 years	114 (96%)	113 (94%)	73 (71%)	38 (95%)
65 + years	5 (4%)	4 (3%)	5 (6%)	2 (5%)
Gender				
Male	94 (79%)	89 (75%)	57 (71%)	27 (68%)
Female	25 (21%)	30 (25%)	23 (29%)	13 (32%)
Race				
White	73 (61%)	68 (57%)	50 (63%)	24 (60%)
Black or Afric.-Amer.	25 (21%)	34 (29%)	19 (24%)	8 (20%)
Am Ind./AK native	16 (13%)	14 (12%)	8 (10%)	4 (10%)
Other	5 (4%)	3 (3%)	3 (4%)	4 (10%)
	Randomized			
	Econazole Foam N=119	Vehicle Foam N=119	Econazole Cream N=80	Vehicle Cream N=40
Ethnicity				
Hispanic or Latino	51 (43%)	47 (39%)	32 (40%)	12 (30%)
Not Hispanic or Latino	68 (57%)	72 (61%)	48 (60%)	28 (70%)
Geographic Region				
United States	119 (100%)	119 (100%)	80 (100%)	40 (100%)
	MITT			
	Econazole Foam N=91	Vehicle Foam N=83	Econazole Cream N=52	Vehicle Cream N=30
Age (years)				
Mean	39.7	42.4	41.6	38.6
Range	19-87	12-71	18-89	19-71
<18 years	0 (0%)	2 (2%)	0 (0%)	0 (0%)
18 to 64 years	88 (97%)	77 (93%)	49 (94%)	29 (97%)

65 + years	3 (3%)	4 (5%)	3 (6%)	1 (3%)
Gender				
Male	71 (78%)	65 (78%)	38 (73%)	22 (73%)
Female	29 (22%)	18 (22%)	14 (27%)	8 (27%)
Race				
White	55 (60%)	53 (64%)	32 (62%)	18 (60%)
Black or Afric.-Amer.	21 (23%)	21 (25%)	15 (29%)	6 (20%)
Am Ind./AK native	12 (13%)	8 (10%)	3 (6%)	4 (13%)
Other	3 (3%)	1 (1%)	2 (4%)	2 (6%)
Ethnicity				
Hispanic or Latino	39 (43%)	33 (40%)	18 (35%)	11 (37%)
Not Hispanic or Latino	52 (57%)	50 (60%)	34 (65%)	19 (63%)
Geographic Region				
United States	91 (100%)	83 (100%)	52 (100%)	30 (100%)

Source: pg 64-65 of study report for Study 303 and Agency statistical review

In Study 303, approximately 60% of the subjects were white and 24% were black or African-American. Approximately 40% of the subjects reported their ethnicity as Hispanic or Latino.

Comment: Subjects in both studies are equally distributed across treatment arms by race and gender which allows for assessment of treatment effect across these subsets. The extreme age ranges (<17 years and >65 years) are underrepresented. However, there is no expectation that there should be a clinical difference in the disease or response to topical antifungal treatment based on age.

Demographics of baseline disease were also collected. The most common pathogen was *T. rubrum*, which was found in 85-90% of the positive baseline cultures. The remaining identified organisms were *E. floccosum*, *T. mentagrophytes, and T. tonsurans.* The baseline severity of erythema and scaling was generally balanced across treatment arms.

Table 9: Baseline Disease Characteristics in MITT Population (study 302)

		Econazole Foam N=82	Vehicle Foam N=83
Fungal culture result			
T. rubrum		69 (84%)	71 (86%)
E. floccosum		8 (10%)	7 (8%)
T. mentagrophytes		5 (6%)	3 (4%)
T. tonsurans		0 (0%)	1 (1%)
T. rubrum/T. mentag.		0 (0%)	1 (1%)
KOH Positive		82 (100%)	83 (100%)
Erythema	*Mild*	30 (37%)	28 (34%)
	Moderate	50 (61%)	48 (58%)

	Severe	2 (2%)	7 (8%)
Scaling	*Moderate*	68 (83%)	65 (78%)
	Severe	17 (17%)	19 (22%)
Cumulative Sign/Symptom Score[1]			
Mean (Std. Dev.)		9.0 (2.53)	9.0 (2.39)
Median		9	9
Range		4 - 16	4 - 16

[1] Sum of erythema, scaling, fissuring, maceration, vesiculation, and pruritus each graded from 0 to 3.
Source: pg 57 of study report for Study 302 and Agency statistical analysis.

Table 10: Baseline Disease Characteristics in MITT Population (study 303)

		Econazole Foam N=91	Vehicle Foam N=83	Econazole Cream N=52	Vehicle Cream N=30
Fungal culture result					
T. rubrum		83 (91%)	75 (90%)	46 (88%)	30 (100%)
E. floccosum		5 (5%)	2 (2%)	2 (4%)	0 (0%)
T. mentagrophytes		2 (2%)	6 (7%)	4 (8%)	0 (0%)
T. rubrum/E. floccosum		1 (1%)	0 (0%)	0 (0%)	0 (0%)
KOH Positive		91 (100%)	83 (100%)	52 (100%)	30 (100%)
Erythema	*None*	0 (0%)	0 (0%)	1 (2%)	0 (0%)
	Mild	32 (35%)	29 (35%)	17 (33%)	8 (27%)
	Moderate	57 (63%)	49 (59%)	31 (60%)	22 (73%)
	Severe	2 (2%)	5 (6%)	3 (6%)	0 (0%)
Scaling	*Moderate*	73 (80%)	64 (77%)	43 (83%)	23 (77%)
	Severe	18 (20%)	19 (23%)	9 (17%)	7 (23%)
Cum. Sign/Symptom Score[1]					
Mean (Std. Dev.)		8.6 (3.14)	8.5 (3.03)	8.3 (2.48)	8.4 (2.99)
Median		8	8	9	8
Range		3-16	3-15	3-13	3-16

[1] Sum of erythema, scaling, fissuring, maceration, vesiculation, and pruritus each graded from 0 to 3.
Source: pg 74-75 of study report for Study 303 and Agency statistical analysis.

Comment: Disease characteristics in both studies are equally distributed across treatment arms. T. rubrum is the pathogen most commonly isolated in association with tinea pedis. As expected, the majority of disease isolates in both studies are t. rubrum which supports the indication for tinea pedis.

6.1.3 Subject Disposition

Study 302 randomized 132 subjects to Econazole Nitrate Foam, 1% and 135 subjects to vehicle foam. Of these subjects, 82 in the econazole foam arm and 83 in the vehicle foam arm had positive baseline cultures and were included in the MITT population.

The most common reason for study discontinuation was negative baseline culture. The next most common reason was lost to follow-up.

Table 11: Subject Disposition (study 302)

	Econazole Foam	Vehicle Foam
Subjects Randomized	132	135
Subjects in MITT	82 (62%)	83 (61%)
Subjects Completed	78 (59%)	80 (59%)
Subjects Discontinued	54 (41%)	55 (41%)
Reasons for discontinuation		
Negative baseline culture	47 (36%)	51 (38%)
Adverse event	0 (0%)	1 (1%)
Subject request	1 (1%)	0 (0%)
Non-compliance	1 (1%)	0 (0%)
Lost to follow-up	4 (3%)	3 (2%)
Other	1 (1%)	0 (0%)

Source: Agency statistical review

Study 303 randomized 119 subjects to Econazole Nitrate Foam, 1%, 119 subjects to vehicle foam, 80 subjects to econazole cream, and 40 subjects to vehicle cream. Of these subjects, 91 econazole foam and 83 vehicle foam subjects had positive baseline cultures and were included in the MITT population. The most common reason for study discontinuation was negative baseline culture. The next most common reason was lost to follow-up.

Table 12: Subject Disposition (study 303)

	Econazole Foam	Vehicle Foam	Econazole Cream	Vehicle Cream
Subjects Randomized	119	119	80	40
Subjects in MITT	91 (77%)	83 (70%)	52 (65%)	30 (75%)
Subjects Completed	82 (69%)	76 (64%)	49 (61%)	28 (70%)
Subjects Discontinued	37 (31%)	43 (36%)	31 (39%)	12 (30%)
Reasons for discontinuation				
Negative baseline culture	25 (21%)	31 (26%)	26 (33%)	9 (23%)
Adverse event	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Subject request	2 (2%)	2 (2%)	2 (3%)	1 (3%)
Investigator decision	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Non-compliance	2 (2%)	2 (2%)	0 (0%)	0 (0%)
Lost to follow-up	6 (5%)	4 (3%)	2 (3%)	0 (0%)
Other	1 (1%)	4 (3%)	1 (1%)	1 (3%)

Source: Agency statistical review

Comment: The studies had a high attrition rate (30-40%). However, most discontinuations were due to a negative culture result which was expected and had been taken into account in study design to minimize the impact on statistical power. Sensitivity analyses were planned to account for missing data and minimize potential bias. Sensitivity analyses are discussed in section 6.1.4.

6.1.4 Analysis of Primary Endpoint(s)

For both phase 3 trials the primary endpoint was complete cure at Day 43 (2 weeks post-treatment) (scores of 0 [none] on all signs and symptoms, negative KOH, and negative culture). Econazole Nitrate Foam, 1% was superior to vehicle foam on the primary efficacy endpoint at Day 43 in both studies (p<0.001). For the MITT analysis, the primary method of handling missing data was LOCF. The results of the MITT and per protocol analyses were similar.

Table 13: Complete Cure Rates at Day 43 (study 302)

	Econazole Foam	Vehicle Foam	P-value
MITT	19/82 (23%)	2/83 (2%)	<0.001
Per Protocol	18/75 (24%)	2/75 (3%)	<0.001

Source: pg 60 of study report for Study 302

Table 14: Complete Cure Rates at Day 43 (study 303)

	Econazole Foam	Vehicle Foam	Econazole Cream	Vehicle Cream	P-value
MITT	23/91 (25%)	4/83 (5%)	17/52 (33%)	1/30 (3%)	<0.001
Per Protocol	16/63 (25%)	4/67 (6%)	16/45 (36%)	1/22 (5%)	<0.001

Source: pg 80-81 of study report for Study 303

Each of the sensitivity analyses proposed by the applicant led to estimated treatment effects that were the same as or larger than the treatment effect estimates produced by LOCF impuation (with the exception of the '95% Bound' imputation in Study 302 which decreased by 2%). In both studies, the treatment effect for complete cure remains statistically significant even when such an imputation is used.

Comment: The primary endpoint showed statistically significant superiority of Econazole Nitrate Foam 1% versus vehicle. Sensitivity analyses demonstrated that conclusions are not driven by the method of handling missing data.

6.1.5 Analysis of Secondary Endpoints(s)

The protocols specified two secondary endpoints: 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). Both secondary endpoints were assessed for econazole foam versus vehicle foam and evaluated at Day 43. To control for multiplicity, the secondary endpoints were analyzed in sequential order (mycological cure followed by effective treatment).

Table 15: Secondary Endpoint analysis at day 43 (study 302)

	Econazole Foam N=82	Vehicle Foam N=83	P-value
Mycological Cure	56 (68%)	13 (16%)	<0.001
Effective Treatment	40 (49%)	9 (11%)	<0.001

Source: pg 62 of study report for Study 302.

Table 16: Secondary Endpoint analysis at day 43 (study 303)

	Econazole Foam N=91	Vehicle Foam N=83	Econazole Cream N=52	Vehicle Cream N=30	P-value
Mycological Cure	61 (67%)	15 (18%)	33 (63%)	1 (3%)	<0.001
Effective Treatment	44 (48%)	9 (11%)	27 (52%)	1 (3%)	<0.001

Source: pg 83 of study report for Study 303.

The mycological cure and effective treatment rates are statistically significant and the results are consistent with the complete cure results.

Comment: The analysis of two pre-specified secondary endpoints showed statistically significant superiority of Econazole Nitrate Foam 1% versus vehicle. Both secondary endpoint outcomes support the primary efficacy assessment and have been previously included in labeling of other topical antifungal products. This reviewer concurs with including these secondary endpoints in labeling as it they may be useful to inform prescribers and match precedent labels for similar products for the indication of interdigital tinea pedis.. Although these secondary endpoints are a slightly lower standard than the primary endpoint, the outcome of "effective treatment" may be desirable to some patients.

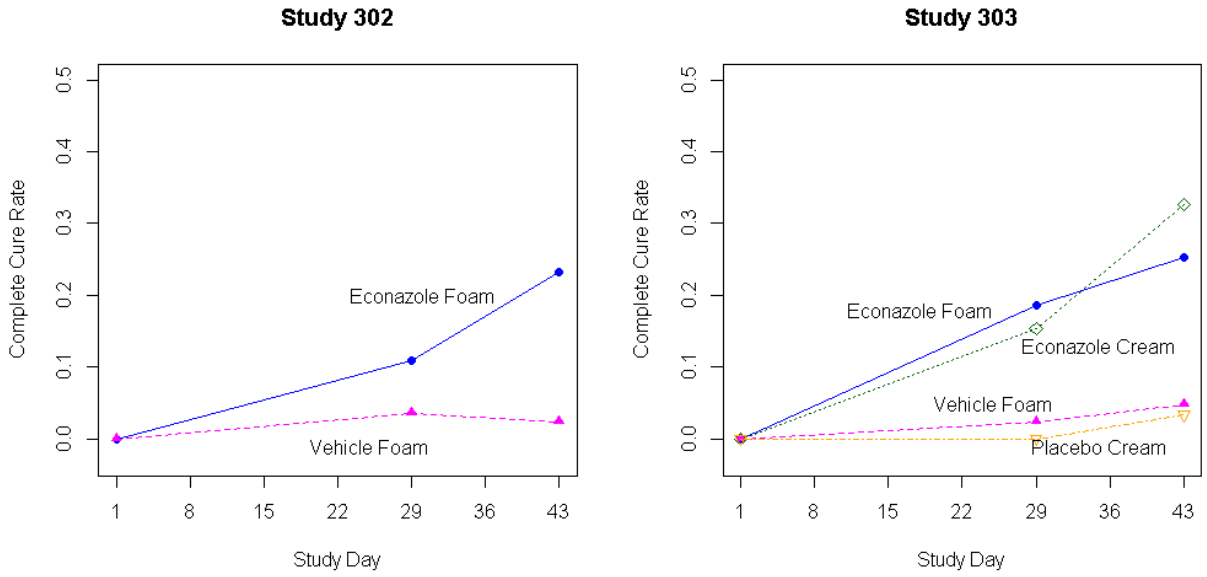
6.1.6 Other Endpoints

KOH and culture were assessed at three time points (baseline and Days 29 and 43). Signs and symptoms (erythema, scaling, fissuring, maceration, vesiculation, and pruritus) were assessed on a scale from 0 to 3 at each visit. This data collection allows

the analysis of complete cure over time with three time points (figure 1) and also changes in signs and symptoms scores over time with five time points (figures 2 and 3).

The difference in the complete cure rate between Econazole Nitrate Foam, 1% and vehicle foam increased between Day 29 and Day 43. The results were similar for the two studies.

Figure 1: Complete Cure over Time

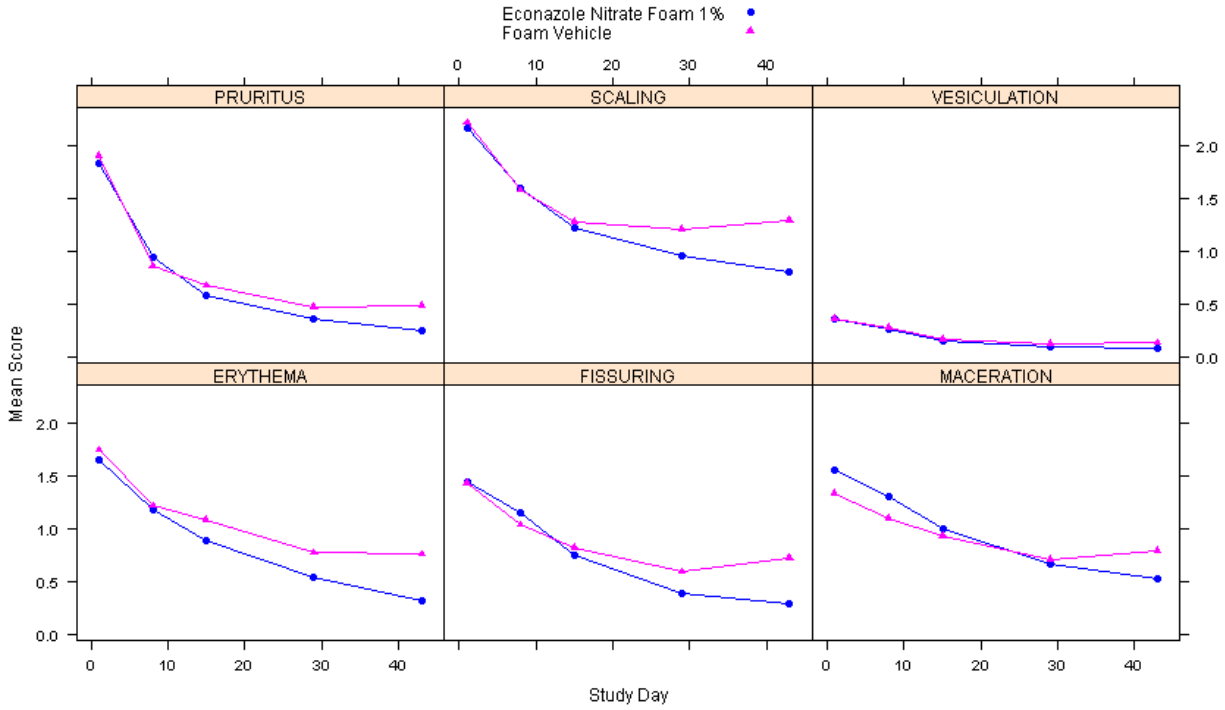


Source: Agency statistical review

Comment: The increased cure rate seen after discontinuation of treatment is consistent with changes in cure rate seen with econazole nitrate cream and supports the adequacy of treatment duration for 4 weeks.

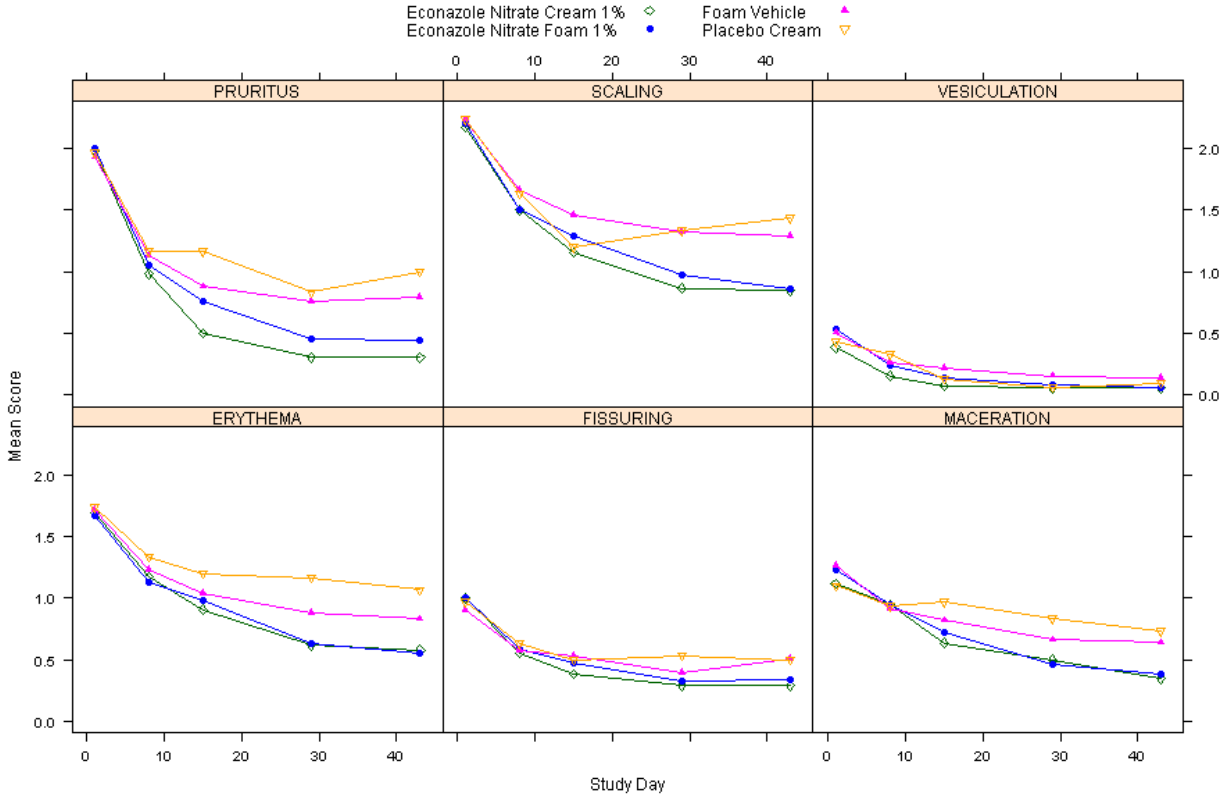
Signs and symptoms decreased on average during the study on all treatment arms, but the decrease was greater on the econazole arms than the vehicle arms.

Figure 2: Mean score of Individual Signs and Symptoms over Time (study 302)



Source: Agency statistical review

Figure 3: Mean score of Individual Signs and Symptoms over Time (study 303)



Source: Agency statistical review

Comment: Improvement in signs and symptoms across all treatment arms is likely due to improved foot care as a result of participating in a clinical trial. Although artificial factors resulting from participation in a clinical trial may impact outcome and minimize the treatment effect, Econazole Nitrate Foam, 1% was able to demonstrate a statistically significant difference over vehicle.

6.1.7 Subpopulations

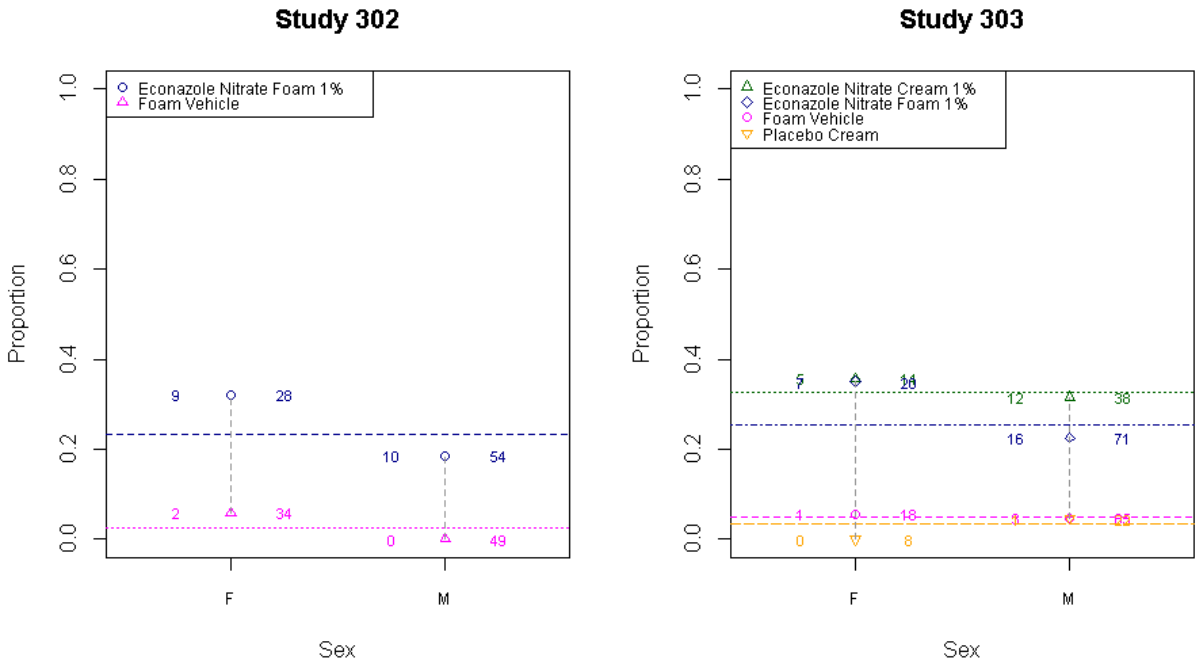
Subgroups were analyzed for complete cure rates, as this is regarded the most clinically meaningful treatment outcome. Treatment effects were generally consistent across gender, race, age and country subgroups, although some subgroups were small and there was some variability in magnitude.

Comment: The trials were not designed and powered to detect treatment differences in subgroup analysis. Analysis of these subgroups was not preplanned and no adjustments for error rates were made. Subgroup analyses are supportive of the primary analysis but do not provide an adequate basis for definitive conclusions. Therefore, it is this reviewer's opinion that subgroup analyses do not provide substantial evidence for inclusion in labeling.

Gender

Econazole Nitrate Foam 1% was superior to vehicle foam in both males and females.

Figure 4: Complete Cure Rate by Gender

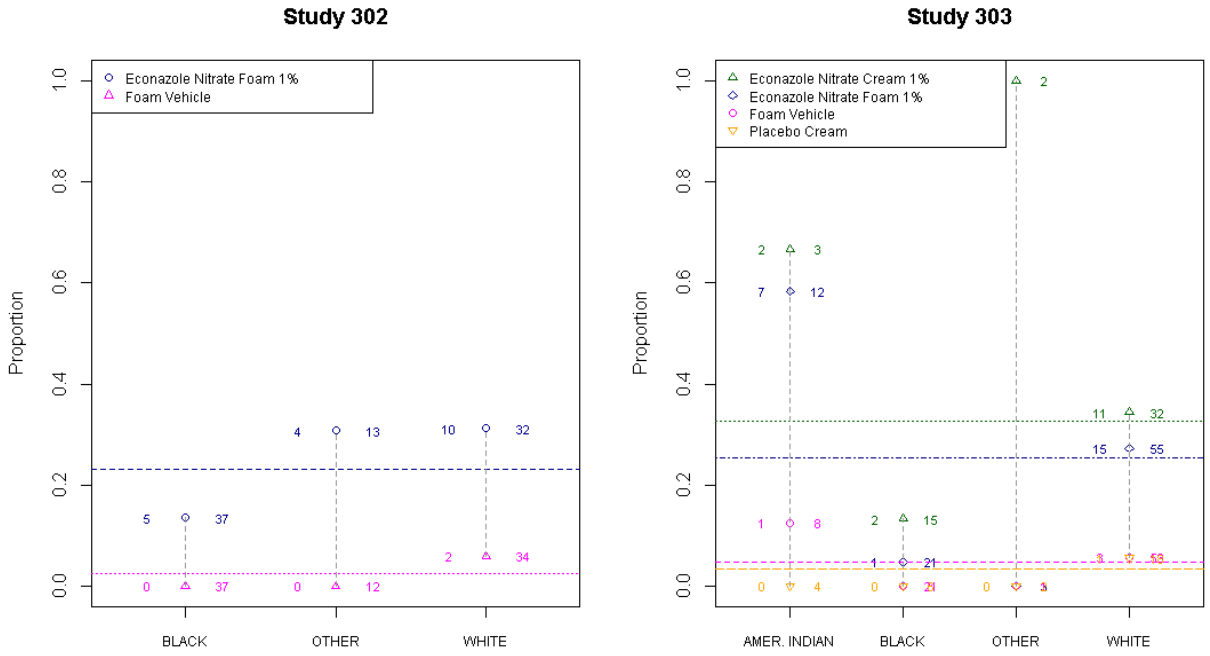


Source: Agency statistical review

Race

Econazole Nitrate Foam 1% was superior to vehicle foam across all races.

Figure 5: Complete Cure Rate by Race



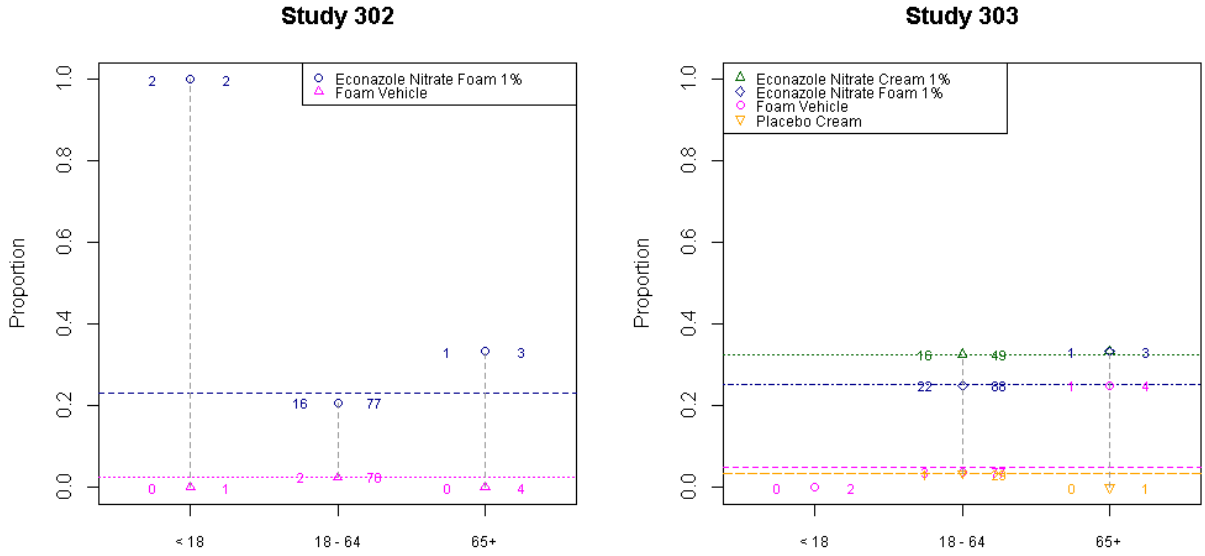
Source: Agency statistical review

Comment: Some race subgroups were small and there was some variability in magnitude. However, the direction (not the magnitude) of the treatment effect within each race was the same as is expected for this type of analysis.

Age

Econazole Nitrate Foam 1% was superior to vehicle foam across all age groups.

Figure 6: Complete Cure Rate by Age



Source: Agency statistical review

Study enrollment was open to subjects ≥12 years of age. Only 11 subjects who were 12 to18 years of age were randomized; the MITT population included 4 adolescent subjects (2 subjects received Econazole Nitrate Foam 1% and 2 received vehicle foam).

Comment: The number of subjects in 12-18 years of age group is not large enough to draw meaningful conclusion about efficacy. Because the disease characteristics for interdigital tinea pedis are similar between adult and adolescent populations, the efficacy for adolescents can be extrapolated from adult population. It is this reviewer's opinion that efficacy may be extrapolated to support the indication of interdigital tinea pedis in adolescents. Safety to support approval in this population is discussed in section 7.5.3.

For subjects >65 years of age, 27 were randomized; the MITT population included 18 subjects (6 subjects received Econazole Nitrate Foam 1% and 8 received vehicle foam).

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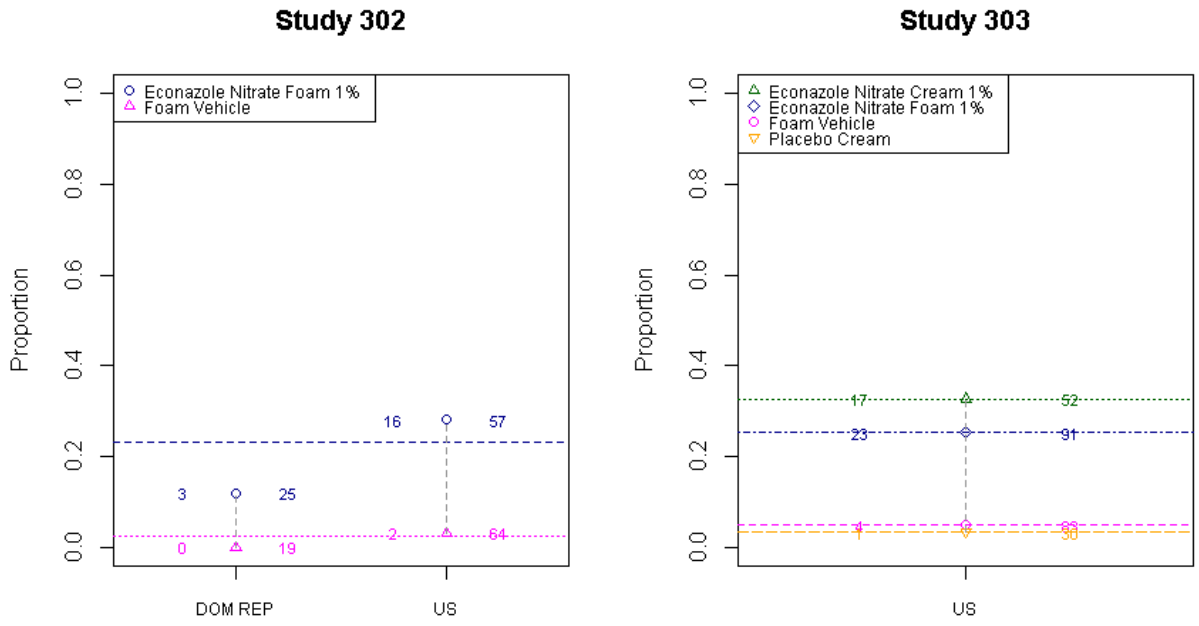
Comment: The number of subjects age 65 years and older is not large enough to draw meaningful conclusion about efficacy. However, there is no expectation that disease or response to treatment will differ in this population. It is this reviewer's opinion that it is not necessary to restrict the indication by age to exclude geriatric patients. Safety to support approval in this population is discussed in section 7.5.3.

Country

Econazole Nitrate Foam 1% was superior to vehicle foam for both county subgroups.

Figure 7: Complete Cure Rate by Country

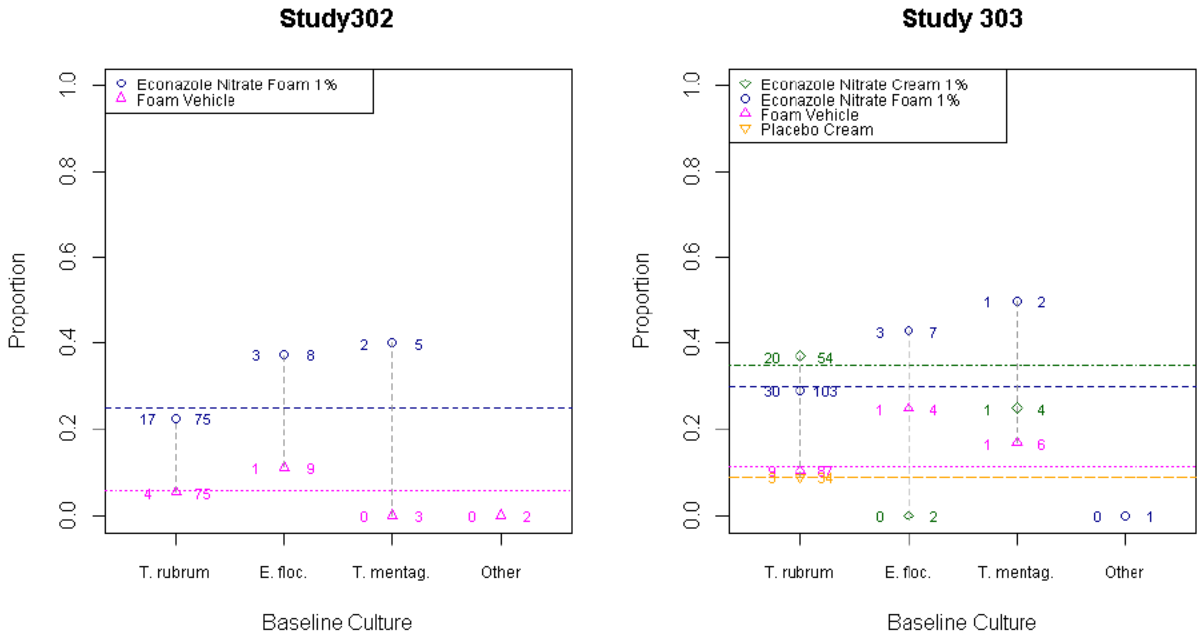


Source: Agency statistical review

Comment: Treatment effect for study 302 was not driven by the non-US site and the study can be used to support efficacy in the US population.

Baseline Pathogen

The most common pathogen was *T. rubrum*, which was found in 85-90% of the positive baseline cultures. 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.



Source: Agency statistical review

The clinical microbiology reviewer also evaluated clinical cure rates in subjects, infected with *T. rubrum*, the most common pathogen, from both US and non-US sites. The analysis showed that clinical cure rates in subjects infected with *T. rubrum* from non-US sites show a trend towards decrease compared to the US sites (14% non-US; ~25% US in either MITT or PP population). However, there was no difference in mycological cure rates or in vitro susceptibility of isolates from US vs. non US sites.

Comment: There were a small number of subjects from the non-US sites compared to the US sites and some variability in magnitude of treatment effect is expected in subgroup analysis. Similar mycological cure rates and in vitro susceptibility suggest similar organisms are present in both US and non-US populations. It is this reviewer's opinion that study 302 can be used to support efficacy in the US population.

The applicant proposes to label Econazole Nitrate Foam, 1% (b) (4) . However, in addition to tinea pedis, econazole nitrate cream is approved for the treatment of other indications (tinea cruris and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Microsporum canis, Microsporum audouini, Microsporum gypseum and Epidermophyton floccosum*, cutaneous candidiasis and in the treatment of tinea versicolor.).

Of the organisms in econazole nitrate cream labeling, *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, and Epidermophyton floccosum* are the pathogens most commonly associated with interdigital tinea pedis. In the clinical trials, the isolated pathogen for the majority of subjects was *Trichophyton rubrum*; there were 15 subjects with *Epidermophyton floccosum*; 7 subjects with *Trichophyton mentagrophytes* and no subjects with *Trichophyton tonsurans.*

Comment: The applicant is seeking approval of Econazole Nitrate Foam, 1% for the treatment of interdigital tinea pedis only. It is this reviewer's opinion that labeling should reflect the organisms commonly associated with the indication and in which at least some subjects have been evaluated. Although there are a small number of subjects with pathogens other than T. rubrum, and the trials were not designed and powered to detect treatment differences in baseline isolate subgroups, some subjects with other baseline isolates achieved complete cure. This reviewer finds this to be supportive and recommends including Trichophyton rubrum, Trichophyton mentagrophytes, ,and Epidermophyton floccosum in labeling (indication and microbiology sections).

It should be noted that the Division of Anti Infective Products (DAIP) usually applies a threshold standard of 10 treated subjects with a specific cultured organism for inclusion in labeling. For this product, Trichophyton mentagrophytes, with 7 subjects treated, would not meet this threshold. It is this reviewer's opinion that treatment of 7 subjects is sufficient to include the pathogen in labeling because T. mentagrophytes has been shown to be associated with tinea pedis and the moiety has been shown to have efficacy against this pathogen. Also, selection of a topical antifungal is less likely than other antimicrobial products to be selected based on organism and is more likely to be selected based on clinical presentation and KOH results. Therefore, this reviewer recommends including T. Mentagrophytes in labeling for this topical antifungal product for the indication of interdigital tinea pedis.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose ranging studies were not performed.

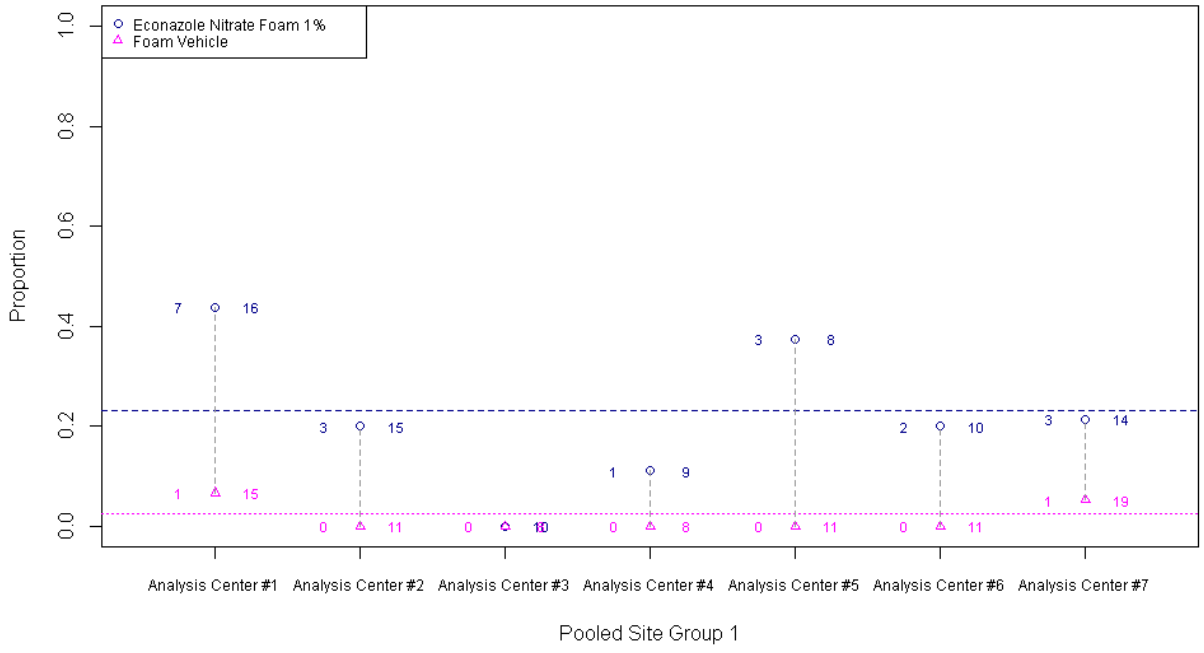
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The efficacy of Econazole Nitrate Foam 1% was demonstrated at day 43 (2 weeks after completion of treatment). Minimum inhibitory concentrations (MICs) of clinical isolates collected prior to initiation of therapy, in the phase 2 and phase 3 clinical trials performed by the applicant, were shown to be same as MICs of isolates collected after 4 weeks of treatment and 2 weeks follow up. No additional follow up for successfully treated subjects was provided, therefore the persistence of efficacy and/or tolerance cannot be established.

6.1.10 Additional Efficacy Issues/Analyses

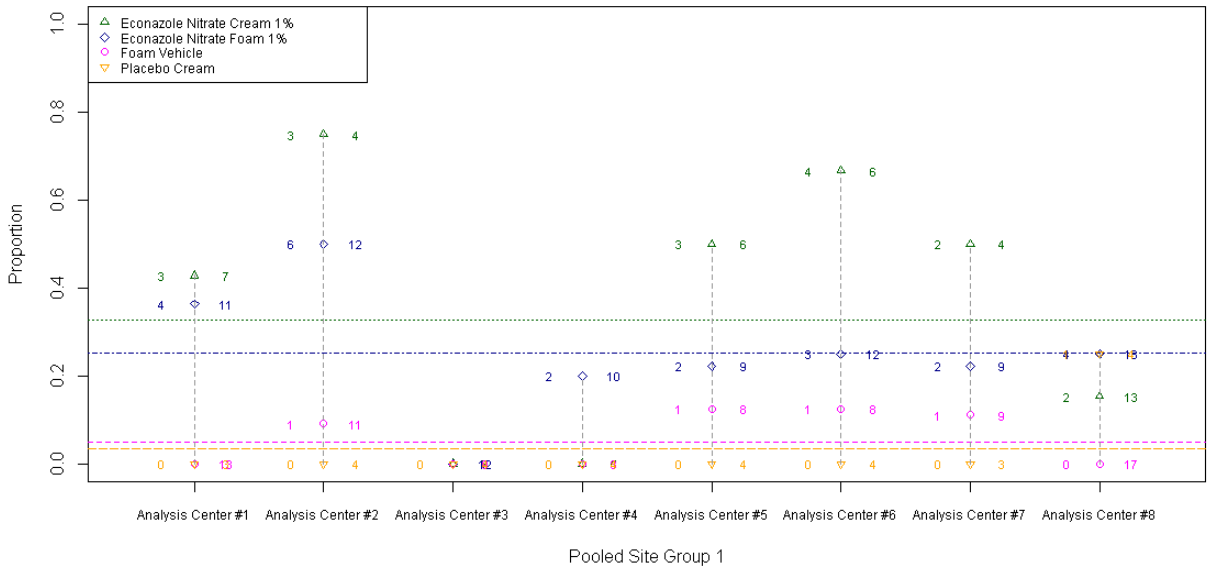
Study 302 was conducted at 14 centers, 12 in the U.S. and 2 in the Dominican Republic. Three of the centers (one in the U.S. and both of the Dominican Republic centers) enrolled at least 8 subjects on the econazole foam and vehicle foam arms, and were not pooled with other centers. The remaining 11 centers were combined into 4 analysis centers (2 to 4 centers per analysis center). Analysis centers 2 and 3 were the Dominican Republic centers; the remaining analysis centers were U.S. centers. Study 303 was conducted at 18 centers, all in the U.S. Two centers enrolled at least 8 subjects on the econazole foam and vehicle foam arms. The remaining 16 centers were combined into 6 analysis centers (2 to 4 centers per analysis center). Treatment effects were generally consistent across analysis centers, and no center is overly influential. The p-values from the Breslow-Day test for homogeneity (econazole foam and vehicle foam arms) were 0.868 for Study 302 and 0.580 for Study 303; neither test identified significant heterogeneity.

Figure 8: Complete Cure Rate by Analysis Center (study 302)



Source: Agency statistical review

Figure 9: Complete Cure Rate by Analysis Center (study 303)



Source: Agency statistical review

7 Review of Safety

Safety Summary

The data base for Econazole Nitrate Foam, 1% 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 Study 303). 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.

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.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There were eight relevant clinical safety studies: four (4) Phase 1 studies (079-2951-104, 079-2951-105, 079-2951-106, and 079-2951-107), two (2) Phase 2 (D79-2902-07 and 079-2951-109) and two (2) Phase 3 studies (079-2951-302 and 079-2951-303).In these studies, Econazole Nitrate Foam, 1% was safe and well-tolerated with a safety profile analogous to the Foam Vehicle

7.1.2 Categorization of Adverse Events

Adverse events were recorded in standard medical terminology, and coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 14.0. This reviewer finds the categorization of AEs acceptable. Because most of the events occurred in a relatively few number of subjects (less than 1% of the subjects in each treatment group) local cutaneous events occurring at application site were lumped together for labeling.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from all eight studies were reviewed. 4 of these studies were dermal safety studies conducted in healthy subjects. These studies mostly provided information regarding local safety under provocative conditions. Safety assessment was limited to local cutaneous reactions and adverse event reporting.

The two PK studies (D79-2902-07 and 079-2951-109) included fewer safety assessments than in the phase 3 trials. Study 07 evaluated local and systemic adverse events at each visit and hematology, serum chemistry, and urinalyses at Baseline and Day 29. Study 109 only evaluated local and systemic adverse events at each visit and no adverse events were reported for this study.

The two Phase 3 studies (079-2951-302 and 079-2951-303) evaluated local and systemic adverse events at each visit and hematology, serum chemistry, and urinalyses at Baseline and Day 29 and day 43.

Additionally, the formulation manufacturing site was changed between conducting study 07 and studies 302 and 303 (and 109). Although the formulations were deemed by the Agency to be successfully bridged in an IVRT study, the formulations resulted in different levels of systemic absorption when compared across the 2 PK studies conducted in different populations.

Due to the more extensive safety evaluation and potentially higher systemic exposure in the phase 3 trials, these studies were pooled for the majority of the safety assessments.

7.2 Adequacy of Safety Assessments

Econazole nitrate has been marketed in the United States since approved as cream formulation in 1982. The cream is approved as a once daily application for the topical treatment of tinea pedis, tinea cruris and tinea corporis. Therefore, the cream formulation is more likely to be used on a larger body surface area and in younger children than the Econazole Nitrate Foam, 1%.

Since this product is relying on the safety of the cream formulation, this reviewer finds the safety assessments conducted for econazole nitrate foam for the indication of tinea pedis adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

28 treatment applications were planned in the phase 3 studies and the mean and median number of applications of all treatment arms in both study 302 and 303 was close to 28. The minimum number of applications among subjects known to have applied treatment at least once was 5 applications, and the maximum was 45.

The amount of study product used was more variable. The mean amount of econazole foam used was about 65 g, while the median was about 50 g and the maximum amount was 216 g. The amounts of vehicle foam used were similar.

Table 17: Extent of Exposure (study 302)

	Econazole Foam N = 130	Vehicle Foam N = 134
Number of Applications	*N=127*	*N=132*
Mean (SD) Median Range	27.4 (3.13) 28 5 to 43	27.6 (3.01) 28 6 to 40
Amount used (g)	*N=122*	*N=128*
Mean (SD) Median Range	65.6 (43.62) 51.5 5 to 198	73.2 (49.54) 59.3 7 to 231

Source: pg 86 of study report for Study 302.

Table 18: Extent of Exposure (study 303)

	Econazole Foam N = 116	Vehicle Foam N = 115	Econazole Cream N=79	Vehicle Cream N=40
Number of	*N=114*	*N=113*	*N=78*	*N=39*

Applications				
Mean (SD) Median Range	28.1 (4.14) 28 7 to 45	27.8 (3.99) 28 6 to 44	28.2 (2.98) 28 14 to 42	28.2 (3.57) 28 16 to 43
Amount used (g)	*N=105*	*N=108*	*N=75*	*N=37*
Mean (SD) Median Range	63.6 (43.79) 49.4 7 to 216	65.0 (47.75) 52.3 5 to 221	91.2 (78.20) 63.3 5 to 309	83.3 (88.26) 49.3 7 to 417

Source: pg 119 of study report for Study 303.

Comment: The exposure in subjects treated with foam (active and vehicle) was less than subjects treated with cream (active and vehicle) for both mean and maximum amount used. It is likely due to the foam being easier to spread than the cream. The reasonable consistency of number of applications and variable amount used by subjects in the study is what would be expected for real world use of a topical product. The exposure to Econazole Nitrate Foam, 1% in the clinical studies supports the safety for this product for labeled use of 4 weeks daily in the treatment of interdigital tinea pedis.

7.2.2 Explorations for Dose Response

The applicant did not conduct any dose ranging studies for the 505(b)(2) development of this product. The sponsor did explore the full tinea pedis indication (interdigital and moccasin type) in phase 2 using the 1% formulation. The applicant opted to proceed to Phase 3 with the interdigital indication only based on treatment effects seen in the phase 2 study.

7.2.3 Special Animal and/or In Vitro Testing

In addition to relying upon the Agency's finding of safety for econazole nitrate cream, the applicant 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. No irritation, sensitization, phototoxicity or significant treatment-related toxic effects was demonstrated in these animal studies. Thus, no new potential safety signal was identified based on the animal studies conducted with the foam formulation applied topically in concentrations ranging from 1-4%.

7.2.4 Routine Clinical Testing

The schedule of clinical safety assessments for each of the studies consisted of general physical examination, routine laboratory testing, ECG assessment and monitoring for

AE (local and systemic). The methods and tests used as well as the frequency of testing were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The applicant conducted PK assessment in the following trials:

- 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, clinical pharmacology, reviewed PK data from the study and 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 Cmax (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 Cmax 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 7h 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.

Comment: The PK data demonstrate that the AUC for the foam formulation is slightly higher than the cream formulation. It is this reviewer's opinion that the slight increase in systemic bioavailability is acceptable since the intended labeled use of this product is for tinea pedis only. Econazole nitrate has been marketed in the United States since approved as a cream formulation in 1982 and its safety profile is reasonably characterized. The cream is approved in the US for once daily application in the topical treatment of tinea pedis, tinea cruris and tinea corporis. The systemic exposure from use in tinea cruris and tinea corporis is likely to overlap with the range of exposure for the foam since it is more likely to be used on a larger body surface area and in younger children. Additionally, econazole nitrate is approved for marketing outside of the US for

vaginal application. Systemic absorption via the mucosal surface is more likely to be greater and approximate the exposure seen in the topical foam formulation.

It is not clear to this reviewer as to why pediatric subjects (ages 12-17) had slightly higher exposure than adults with the foam formulation. A significant difference in the permeability of adolescent and adult skin would not be expected as would be seen in younger children. It may be due to the change in formulation manufacturing site which occurred between conducting the adult PK study (07) and the pediatric PK study (109). However, the formulations were deemed by the Agency to be successfully bridged based on an IVRT study. The difference in exposure seen between the adult and pediatric subjects is acceptable to this reviewer based on the rationale provided above and should have negligible clinical impacts.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Econazole nitrate is an imdiazole antifungal that is administered topically. Hepatic dysfunction can develop when azoles are given orally, particularly with ketoconazole. Voriconazole is associated with a number of adverse effects in humans, including vision disturbances.

There were no cases of hepatic dysfunction or visual disturbances identified in the safety population exposed to Econazole nitrate foam.

Other imidazoles include Clotrimazole 1% (Lotrimin, Mycelex, OTC), Miconazole nitrate 2% (Monistat-Derm, Micatin, OTC),Ketoconazole 2% (Nizoral),Oxiconazole nitrate 1% (Oxistat) and Sulconazole (Exelderm) which are administered topically and are marketed both by prescription and over-the-counter. Topically administered imidazole antifungal products, including econazole nitrate cream are generally regarded as safe. The following local adverse reactions have been reported infrequently with topical formulations containing econazole nitrate 1%: stinging, itching, erythema, burning sensation, contact dermatitis and a pruritic rash.

Comment: The applicant's effort to detect specific AEs was adequate. The safety profile appears to be similar to the know safety profile of econazole nitrate cream and other topical imidazole antifungal products, some which are available over-the-counter.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in these studies.

7.3.2 Nonfatal Serious Adverse Events

One SAE, hypertension (which represented a worsening from baseline hypertension) was reported in the Foam Vehicle group in Study 079-2951-302 for one subject; the investigator determined the event was not treatment related and the subject was discontinued from the study

Comment: This reviewer concurs with the investigator that it is unlikely that the SAE was related to the treatment with vehicle.

7.3.3 Dropouts and/or Discontinuations

One Foam Vehicle subject (Study 302) discontinued treatment due to an AE of moderate application dermatitis; one Econazole Nitrate Foam, 1% subject (Study 303) discontinued treatment due to an AE of moderate eczema; one Placebo Cream subject (Study 303) discontinued treatment due to an AE of mild blood glucose increased. In study 07 no subjects in the ITT population discontinued study participation due to an AE

Comment: The 4 weeks up treatment appears to be well-tolerated. This reviewer did not find many subjects discontinuing treatment for an AE or other safety reason. Most discontinuations were due to negative culture results as expected. The small number of discontinuations supports labeling for 4 weeks of treatment.

7.3.4 Significant Adverse Events

Significant AEs identified in study 302 include:

- hypertension (discussed under section 7.3.2 severe AE)—Foam vehicle
- moderate application site dermatitis (discussed under section7.3.3 discontinuation)—Foam vehicle.

In study 303, six AEs, reported among 5 subjects were severe:

- procedural pain (related to hiatal hernia)--Econazole Nitrate Foam 1%
- nephrolithiasis—Foam vehicle
- pain associated with a kidney —Foam vehicle
- musculoskeletal pain—Foam vehicle
- bronchitis--Placebo Cream

Comment: No other significant AEs were identified for subjects treated with econazole nitrate foam or vehicle foam.

7.3.5 Submission Specific Primary Safety Concerns

There were no clinically meaningful trends observed for any of the liver function parameters evaluated in the phase 3 studies.

No application site reactions were reported for Econazole Nitrate Foam, 1%. Application site reactions were identified in subjects treated with foam vehicle including application site pain and dermatitis.

Comment: This reviewer is not recommending labeling regarding liver toxicity or monitoring for this topical imidazole antifungal based on safety findings in the development program. This reviewer is recommending labeling for application site reactions as the topical irritation may be due to excipients present in vehicle and may emerge with use of the drug product as well as it becomes more widely used.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Similar proportions of Econazole Nitrate Foam, 1% 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.

Table 19: Adverse Events (study 302)

	Econazole Foam N = 130	Vehicle Foam N = 134
Any Adverse Event	17 (13.1%)	16 (11.9%)
Gastrointestinal disorders (Oral pain)	1 (0.8%)	0 (0.0%)
General disorders and administration site conditions (Application site dermatitis)	0 (0.0%)	1 (0.7%)
Infections and infestations	6 (4.6%)	6 (4.5%)
Cystitis	1 (0.8%)	0 (0.0%)
Helicobacter gastritis	1 (0.8%)	0 (0.0%)
Influenza	1 (0.8%)	0 (0.0%)
Nasopharyngitis	2 (1.5%)	4 (3.0%)
Sinusitis bacterial	0 (0.0%)	1 (0.7%)
Upper respiratory tract infection	1 (0.8%)	1 (0.7%)

Injury, poisoning and procedural complications (Ligament injury)	1 (0.8%)	0 (0.0%)
Musculoskeletal and connective tissue disorders (Back pain)	1 (0.8%)	0 (0.0%)
Nervous system disorders (Headache)	6 (4.6%)	6 (4.5%)
Respiratory, thoracic and mediastinal disorders	2 (1.5%)	2 (1.5%)
Nasal congestion	1 (0.8%)	0 (0.0%)
Nasal dryness	0 (0.0%)	1 (0.7%)
Oropharyngeal pain	1 (0.8%)	0 (0.0%)
Pulmonary congestion	0 (0.0%)	1 (0.7%)
Rhinorrhea	0 (0.0%)	1 (0.7%)
Vascular disorders (Hypertension)	0 (0.0%)	1 (0.7%)

Source: pg 91 of study report for Study 302

Table 20: Adverse Events (study 303)

	Econazole Foam N=116	Foam Vehicle N=115	Econazole Cream N=79	Vehicle Cream N=40
Any Adverse Event	11 (9.5%)	11 (9.6%)	8 (10.1%)	5 (12.5%)
Ear and labyrinth disorders (Ear pain)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Vomiting	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Gen. disorders and admin. site cond.	0 (0.0%)	3 (2.6%)	0 (0.0%)	0 (0.0%)
Applic. site pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Immune sys. dis. (Hypersensitivity)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Infections and infestations	2 (1.7%)	3 (2.6%)	2 (2.5%)	3 (7.5%)
Bronchitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
Influenza	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
Local infection	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Nasopharyngitis	1 (0.9%)	0 (0.0%)	1 (1.3%)	1 (2.5%)
Oral herpes	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)
Sinusitis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
URTI	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and proced.	3 (2.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)

compl.								
Excoriation	1	(0.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Laceration	1	(0.9%)	1	(0.9%)	0	(0.0%)	0	(0.0%)
Procedural pain	1	(0.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Investigations	0	(0.0%)	1	(0.9%)	2	(2.5%)	2	(5.0%)
Metab. and nutr. dis. (Type 2 diabetes)	0	(0.0%)	1	(0.9%)	0	(0.0%)	0	(0.0%)
Musculo and connective tissue dis.	1	(0.9%)	2	(1.7%)	1	(1.3%)	0	(0.0%)
Back pain	1	(0.9%)	1	(0.9%)	0	(0.0%)	0	(0.0%)
Musculoskeletal pain	0	(0.0%)	1	(0.9%)	1	(1.3%)	0	(0.0%)
Nervous System Disorders (Headache)	1	(0.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Renal and urinary disorders	0	(0.0%)	2	(1.7%)	1	(1.3%)	0	(0.0%)
Hematuria	0	(0.0%)	1	(0.9%)	1	(1.3%)	0	(0.0%)
Nephrolithiasis	0	(0.0%)	1	(0.9%)	0	(0.0%)	0	(0.0%)
Resp., thor. and mediast. disorders (Rhinorrhea)	1	(0.9%)	1	(0.9%)	1	(1.3%)	0	(0.0%)
Skin and subcutaneous tissue disorders	1	(0.9%)	0	(0.0%)	1	(1.3%)	0	(0.0%)
Dermatitis contact	0	(0.0%)	0	(0.0%)	1	(1.3%)	0	(0.0%)
Eczema	1	(0.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Source: pg 126 – 128 of study report for Study 303

Phase 2 study (D79-2902-07) in which subjects also had 4 weeks of treatment had a similar AE profile to the above phase 3 studies. The number of subjects experiencing AEs was comparable across treatment groups. There were 22.2% (10/45), 23.3% (10/43), and 14.9% (7/47) subjects in the Econazole Nitrate Cream 1%, Econazole Nitrate Foam, 1%, and Foam Vehicle treatment groups, respectively, that experienced any AE. No deaths occurred in the study. No subjects discontinued due to an AE. Subjects treated with Econazole Nitrate Foam 1% and Foam Vehicle reported application site reactions including pruritus (Econazole Nitrate Foam) and application site pain and fissures (Foam Vehicle).

Comment: No safety signal was identified based on reported AEs. The most common AEs (headache and nasopharyngitis) are not considered by this reviewer to be related to treatment and thus are not recommended as including as adverse reactions in labeling. It is this reviewer's opinion that the most common adverse reaction is cutaneous reactions occurring at application site. Most application site reactions occurred in the foam vehicle arm (except for 1 report of pruritus). Local cutaneous reactions may be due to excipients present in vehicle and may emerge with use of the drug product as well as it becomes more widely used.

This reviewer recommends lumping together both Econazole Nitrate Foam, 1% *and foam vehicle application reactions for labeling. The recommended language for labeling is as follows:*

> *"During clinical trials with Ecoza 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."*

7.4.2 Laboratory Findings

Overall, there were no clinically meaningful trends observed for any of the laboratory parameters. Study 302 did not identify any significant laboratory abnormalities or AEs of abnormal laboratory values. Study 303 demonstrated shifts (some greater than 15%) from within normal limits at baseline to beyond normal limits at end of treatment or 2 weeks post-treatment. However, these events were uncommon. Each parameter change did not occur in more than one subject and were variable across the different groups (econazole nitrate foam, foam vehicle, econazole nitrate cream, cream vehicle).

Comment: No trend was identified which would pose as a safety concern for approval or warrant labeling.

7.4.3 Vital Signs

Heart rate was assessed at selected sites in study 303 as part of the cardiac assessment. See discussion under 7.4.4 below.

7.4.4 Electrocardiograms (ECGs)

In study 303, electrocardiograms (ECGs) were performed in triplicate based on 12-Lead ECGs taken at approximately 2-minute intervals in a subset of 98 subjects enrolled at four (4) of the twenty-two (22) sites. Thirty-three (33) subjects were randomized to Econazole Nitrate Foam 1%, 33 subjects to the Foam Vehicle, 21 subjects to the Econazole Nitrate Cream 1%, and 11 to the Placebo Cream.

Summary data was provided for absolute QTc interval prolongations, change from baseline in QTc interval, and change from the baseline in heart rate, PR interval, and QRS duration. Some subjects did not complete ECG assessment do to study discontinuation. The subjects evaluated per treatment arm are shown below.

Table 21: Subject Disposition for ECG analysis

	Econazole Foam	Econazole Cream	Foam Vehicle	Placebo Cream

Number with any on Drug ECGs	29	18	29	11
Number Completed Study	25	15	24	7

One subject (03-016) in the Econazole Foam treatment group had a QTcF >450 msec and QTcB >450 msec at each study day, including Day 1 predose baseline. The QTcF increased to 462 msec on Day 29 and 465 msec on Day 43. This subject also had a QTcB greater than 480 msec.

Two subjects in the Econazole Cream treatment group (04-006 on Day 29 and 14-005 on Day 43) each had a single QTcF just above 450 msec.

No subject had a QTcF over 480 msec and there were no subjects that experienced an increase of QTcF more than 30 msec from baseline. The QTcF findings demonstrate small and insignificant increases.

Mean changes from baseline in QRS duration and PR interval remained within normal limits. Mean changes in heart rate from baseline fell in a range of 2.9 to 4.6 beats per minute on all study days. This reviewer finds these changes not to be clinically significant.

Treatment emergent ECG changes were not considered to be clinically significant findings with the exception of QTcB prolongation in the Econazole Nitrate Foam 1% treated subject (03-016) previously discussed above.

This subject 03-016(WJJ) had trough blood levels evaluated. Both baseline and 2 weeks post-treatment level were below the quantifiable limit. Day 29 (end of treatment) level was 216 pg/mL. This subject's finding appears to be an outlier in 25 subjects who were assessed and treated with Econazole Nitrate Foam, 1%. This subject's QTcF was elevated at baseline (457 msec) and the difference in QTcF between day 29 and day 43 (data points which demonstrated the maximum and minimum levels of drug detected) was an increase in 3 msec. The changes do not appear to correlate with systemic drug concentration.

Comment: Given the history of econazole use and the lack of QT related adverse events reported this reviewer concurs with clinical pharmacology that granting a waiver for conducting TQT assessment appears reasonable. It is this reviewer's opinion that no additional labeling pertaining to QTc is necessary based on this one case.

7.4.5 Special Safety Studies/Clinical Trials

Dermal safety was evaluated for phototoxicity, cumulative irritation, photosensitization and sensitization in healthy subjects in the four studies described below.

1. STUDY NUMBER: 079-2951-106: A 4-Day, Randomized Study to Evaluate the Irritation Potential of Econazole Nitrate Foam, 1% and Vehicle when Application to Skin is Followed by Light Exposure in Healthy Volunteers, Using a Phototoxicity Patch Test Design

   This was a single-center, randomized, within-subject comparison study of econazole and vehicle. Each product was applied to 2 sites, (one was irradiated and one remained nonirradiated). The irradiated and nonirradiated sites were compared with each other and with an untreated irradiated site. A defined area (approximately 50 cm2) on the infrascapular region of each subject's back was irradiated to determine the minimal erythemal dose (MED) of ultraviolet (UV) light. All subjects had 4 application sites (2 irradiated and 2 nonirradiated) on the infrascapular region of the back designated for test sample application and irradiation. An additional untreated site was designated for irradiation only. The products were applied to the assigned sites under occlusive conditions. After approximately 24±2 hours, the designated sites, including the untreated site, were exposed to irradiation. The sites were examined at various time points for the purpose of determining the phototoxicity irritation potential of the test preparation. Dermal reactions at the test sites were evaluated using a visual scale that rates the degree of erythema, edema, and other signs of cutaneous irritation.

   32 out of the 33 adult subjects enrolled completed the study. Subjects topically applied 0.6 mL Econazole Nitrate Foam, 1% topically under occlusive patch.

   No evidence of phototoxicity was observed in any subject with the Econazole Nitrate Foam, 1% or vehicle treatments. The investigational products were well tolerated. The majority of subjects (97.0%) did not report any adverse events during the study. Of note, 1 subject reported pruritus.

   Comment: This reviewer finds the study design including the number of evaluable subjects acceptable for the evaluation of phototoxicity. No phototoxicity was demonstrated and no labeling pertaining to phototoxicity is recommended.

2. STUDY NUMBER: 079-2951-104: A 21-Day, Randomized, Controlled Study to Evaluate the Irritation Potential of Econazole Nitrate Foam, 1% and its Vehicle in Healthy Volunteers, Using a Cumulative Irritant Patch Test Design

   This was a randomized, single-center, controlled, within-subject comparison study of the investigational products (econazole nitrate foam, 1% and vehicle), and positive and negative controls under occlusive conditions in healthy volunteers. All subjects had fields designated for the investigational products patches and the positive and negative control patches at 4 randomly assigned, adjacent sites, for the purpose of determining irritation potential. The investigational products and controls were applied to one side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites were assessed clinically using a visual scale that rates the degree of erythema, edema, and other signs of cutaneous irritation.

   34 out of the 37 adult subjects enrolled completed the study. Subjects topically applied 0.6 mL econazole nitrate foam, 1% topically under occlusive patch. A positive control product (0.2% sodium lauryl sulfate solution, 0.2 mL) and a negative control (0.9% saline, 0.2 mL) were included. The investigational products were applied topically 21 times over 3 weeks.

   No evidence of dermal irritation was observed in any subject with the 1% econazole nitrate foam, vehicle or saline treatments. Mean cumulative and total irritation scores were significantly higher ($p<0.001$) with the SLS treatment as expected. No adverse events were reported in this study.

   Comment: This reviewer finds the study design including the number of evaluable subjects acceptable for the evaluation of provocative dermal irritation. No dermal irritation was demonstrated and no labeling pertaining to dermal irritation other than that observed on diseased skin in the clinical trials is recommended.

3. STUDY NUMBER: 079-2951-107: A 6-Week, Randomized Study to Evaluate the Potential of Econazole Nitrate Foam,1% and Vehicle to Induce a Photoallergic Skin Reaction in Healthy Volunteers, Using a Controlled Photopatch Test Design

   This was a single-center, controlled, randomized, within-subject comparison study of the investigational product (Econazole Nitrate Foam, 1%) and vehicle (econazole nitrate vehicle foam) under occlusive patch conditions. Each subject had an area (approximately 50 cm2) defined on

the infrascapular region of the back irradiated to determine the minimal erythemal dose (MED) of UV light. Subjects had 4 application sites (2 irradiated and 2 nonirradiated) on the infrascapular region of the back designated for test sample application and irradiation. The products were applied to the assigned sites under occlusive patch conditions. After approximately 24 hours, the designated sites were exposed to irradiation. These procedures were performed twice weekly over a 3 week Induction Phase (6 applications/irradiation). The sites were examined at various time points for the purpose of determining photoallergic skin reactions. Dermal reactions at the test sites were evaluated using a visual scale that rates the degree of erythema, edema, and other signs of cutaneous irritation. At the end of the Induction Phase, the subjects entered a Rest Period of 10-17 days. At Challenge, subjects had 4 naïve application sites assigned as follows: irradiated econazole, irradiated vehicle, non-irradiated econazole, and non-irradiated vehicle. The products were applied to the assigned sites under occlusive patch conditions. After approximately 24 hours, the designated sites were exposed to irradiation. In addition, one untreated site was irradiated. All sites were examined for dermal reactions at approximately 24, 48, and 72 hours post irradiation.

57 out of the 59 adult subjects enrolled completed the study. Subjects topically applied 0.6 mL Econazole Nitrate Foam, 1% or vehicle foam topically under occlusive patch 7 times over a 6 week period (6 times during the Induction Phase, and once at Challenge).

No evidence of photosensitization was observed in any subject with the irradiated econazole or irradiated vehicle treatments. During the Challenge Phase, no significant difference ($p=0.417$) in mean dermal response scores was observed with the irradiated econazole or irradiated vehicle treatments when compared to the untreated irradiated control. No photosensitization was observed with either the irradiated econazole or irradiated vehicle treatments as irradiated scores approximated those of untreated control.

Six subjects reported a total of 6 adverse events, each of which are common ailments and are unlikely to be related to study treatment. No subject was discontinued from the study due to an adverse event.

Comment: This reviewer finds the study design including the number of evaluable subjects acceptable for the evaluation of photosensitization. No photosensitization was demonstrated and no labeling pertaining to photosensitization is recommended.

4. STUDY NUMBER: 079-2951-105: A Randomized, Controlled Study to Evaluate the Sensitizing Potential of Econazole Nitrate Foam, 1% in Healthy Volunteers Using a Repeat Insult Patch Test Design.

This was a randomized, single-center, controlled, within-subject comparison study of econazole, vehicle and a positive control and negative control under occlusive conditions, in healthy volunteers. All subjects had each study product (investigational products, positive control, and negative control) applied to randomly assigned, adjacent sites, for the purpose of determining sensitization potential. During the Induction Phase of the study, the investigational products and controls were applied to adjacent sites on the infrascapular area of the back. Evaluation of dermal reactions at the application sites were assessed clinically using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation. Following Induction, subjects had a 10 to 14-day resting phase, after which they entered the Challenge Phase, which consisted of one 48-hour patch application to a naive site on the opposite side of the back. Dermal response during the Challenge Phase provided the basis for an interpretation of contact sensitization.
226 out of the 250 adult subjects enrolled completed the study. Subjects topically applied 0.6 mL Econazole Nitrate Foam, 1% topically under occlusive patch. A positive control product (0.2% sodium lauryl sulfate solution, 0.2 mL) and a negative control (0.9% saline, 0.2 mL) were included. A total of 10 patch applications were made over a period of approximately 6-8 weeks (9 times during the Induction Phase, and once at Challenge). Dermal sensitization analysis was performed for the Completed population.

No evidence of dermal sensitization was observed in any subject with the Econazole Nitrate Foam, 1%, vehicle or saline treatments. Mean dermal response scores were significantly higher ($p<0.001$) with the SLS treatment as expected. One AE was reported and is not likely to be related to the treatment. No subject was discontinued from the study due to an adverse event.

Comment: This reviewer finds the study design including the number of evaluable subjects acceptable for the evaluation of dermal sensitization. No dermal sensitization was demonstrated and no labeling pertaining to dermal sensitization is recommended.

7.4.6 Immunogenicity

This drug product is not expected to induce systemic immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was only one drug concentration and only one dosing regimen applied in these studies, thus dose dependency could not be explored.

7.5.2 Time Dependency for Adverse Events

Time dependency for AEs was not explored.

7.5.3 Drug-Demographic Interactions

The majority of subjects evaluated in the phase 3 clinical studies were between 18 and 64 years of age.

Table 22: Age Demographics in Safety Population (studies 302 and 303)

Age (years)	Foam Vehicle (N=249)	Econazole Nitrate Foam, 1% (N=246)	Total (N=495)
<18 years	5 (2.0%)	4 (1.6%)	9 (1.8%)
18 to 64 years	234 (94.0%)	232 (94.3%)	466 (94.1%)
≥65 years	10 (4.0%)	10 (4.1%)	20 (4.0%)

Source: pg 43 ISS table 22

Of the 173 subjects which completed the phase 3 studies, 2 subjects were between 12-17 years of age and 6 subjects were 65 years of age and older. The pediatric and geriatric populations are small. Reported AEs and safety assessments did not show any significant differences between the age groups.

The applicant has conducted a pediatric PK trial (109) under maximal use conditions in subjects 12 to 17 years of age with interdigital tinea pedis. No adverse events were reported for this trial.

Table 23: Demographics of MITT Pediatric Subjects (study 109)

Age (years)	Econazole Nitrate Foam, 1% (N=25)	Econazole Nitrate cream, 1% (N=25)	Total (N=50)
mean	14.2	14.8	14.5
median	14.0	16.0	14.5
range	12-17	12-17	12-17

Source: pg 36 ISS table 18

The applicant has also conducted an adult PK trial (2-07) under maximal use conditions in subjects 18 years of age and older with interdigital and moccasin type tinea pedis.

The mean, media and range for age of subjects treated with Econazole Nitrate Foam, 1% in this study were 45.9, 43, and 20-82 years respectively. Few subjects were above 65 years of age. Reported AEs and safety assessments did not show any significant differences between the age groups.

Comment: Safety data in pediatrics, albeit in a limited number of subjects, supports 4 weeks of use for the indication of interdigital tinea pedis. This reviewer finds this limited amount of safety data acceptable for approval down to age 12 given the long history of topical Econazole Nitrate Cream. Econazole nitrate has been marketed in the United States since approved as a cream formulation in 1982 and its safety profile is reasonably characterized. The cream is approved in the US for once daily application in the topical treatment of tinea pedis, tinea cruris and tinea corporis without an age restriction. Younger children and children with greater BSA than would be involved in interdigital tinea pedis have likely been exposed to econazole nitrate without a reported significant risk. Recommended labeling for section 8.4:

> *Pediatric use: Of the 173 subjects treated with Ecoza, 1% in clinical studies, 2 subjects were 12-17 years of old. In a pediatric maximal use trial, Ecoza Foam, 1% was applied once daily to eighteen subjects (aged 12-17 years) with interdigital tinea pedis for 28 days. The safety findings for subjects 12 to 17 years were similar to those in the adult population.*

Safety data in geriatrics, also limited, supports 4 weeks of use for the indication of interdigital tinea pedis. This reviewer finds this limited amount of safety data acceptable for approval for geriatric use. However, this older population is more like to have concomitant diseases and medications. Thus, there is a potential risk for drug-drug interactions in this population. Of particular concern to this reviewer is a potential drug interaction with warfarin. See section 7.5.5 below. Recommended labeling for section 8.5:

> *Geriatric use: Of the 173 subjects treated with Ecoza Foam, 1% in clinical studies, 6 subjects were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.*

7.5.4 Drug-Disease Interactions

Drug disease interaction was not explored.

7.5.5 Drug-Drug Interactions

No evaluations of drug-drug interactions were conducted as part of the developmental program. However, there have been cases of drug interactions between topical

econazole nitrate cream and coumarins (warfarin and acenocoumarol) reported in the FDA Adverse Event Reporting System (FAERS) and medical literature.

Econazole is an azole antifungal that acts by blocking 14-alpha demethylation of lanosterol, which is cytochrome P-450 dependent, leading to interference with ergosterol biosynthesis in fungi. Because coumarin anticoagulants are also metabolized via the cytochrome P-450 system, the serum concentration of warfarin may be increased which may result in higher risk of bleeding.

The Division of Dermatology and Dental Product initiated a safety review of drug-drug interaction cases to determine whether a labeling update is warranted for topical econazole nitrate cream. A search of the AERS database found 18 total cases and 3 publications fitting such drug-drug interactions description. The reviewer's assessments of the 18 cases determined that four cases strongly supported the assessment as drug-drug interaction and the cases presented in the publications provided stronger evidence linking the over-anticoagulation to the drug-drug interaction between coumarin therapy and topical econazole treatment.

The clinical reviewer and the OCP reviewer both recommended a labeling update for topical econazole product to inform health care practitioners and patients about the potential interaction between warfarin (coumarin or acenocoumarol) and topical econazole treatment. .See Dr. Gary Chiang's 11/28/12 Clinical review and Dr. An-Chi Lu's 8/28/12 Clinical pharmacology review under NDA 18-751 for Spectazole (econazole nitrate) Cream, 1%.

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. Current labeling for econazole nitrate cream does not include drug interaction information. The owner of Spectazole, who is no longer marketing the innovator product, has been requested to add drug interaction language to its label in order to support the addition of the language to multiple generic labels.

No cases of warfarin interaction have been identified in the development program for the econazole foam formulation.

Comment: The relevance of the drug interaction findings with warfarin/ econazole nitrate cream to the econazole nitrate foam product is not clear. However, given the biological plausibility, antifungal interaction warnings in the warfarin label and increased systemic absorption of the foam formulation as compared to the cream, this reviewer is recommending similar labeling changes regarding drug-drug interactions with warfarin are included as class labeling in the econazole nitrate foam product's label. This reviewer does not find the potential for this interaction to be an approvability issue for

this product. It is also this reviewer's opinion that it is unnecessary to elevate the potential drug-drug interaction language to warnings and precautions due to lack of data/ reports with this particular product. Many things alter warfarin levels (antibiotics, diet etc...) and the effect on anticoagulation can be monitored. Providing this type of class labeling may inform providers to adjust monitoring/ dose for patients on Coumadin and econazole nitrate.

Recommended language for Section 7 is the following:

> *Concomitant administration of econazole and warfarin has resulted in enhancement of anticoagulant effect. Most cases reported product application with use under occlusion, genital application, or application to a large body surface area which may increase the systemic absorption of econazole nitrate. Monitoring of International Normalized Ratio (INR) and/or prothrombin time may be indicated especially for patients who apply econazole to large body surface areas, in the genital area, or under occlusion.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

To date there is no human carcinogenicity data for econazole nitrate. Long-term animal studies to determine the carcinogenic potential of Econazole Nitrate Foam 1% have not been performed.

7.6.2 Human Reproduction and Pregnancy Data

No trials with Econazole Nitrate 1% were conducted in pregnant women. There were no pregnancies reported in the trials.

Econazole Nitrate is category C pregnancy risk based on non-clinical data.

Comment: Econazole Nitrate Foam 1% should be labeled to reflect the lack of data available for use in pregnant or lactating women. Pregnancy category should include that the drug should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

The application triggers PREA as a new dosage form. The applicant submitted a request for a partial waiver of pediatric studies in children 11 years of age and younger and provided the following justification:

1. Drug product does not represent a meaningful therapeutic benefit over existing treatments for children 11 years of age and younger. Currently available over-the-counter drug products, such as Lotrimin Cream and Lotrimin Lotion (clotrimazole 1%) are labeled for treatment of tinea pedis for both adults and children. Accordingly, such over-the-counter drug products provide reasonable, readily available alternatives for the treatment of tinea pedis in children 11 years of age and younger.

2. Drug product is not likely to be used in a substantial number of children 11 years of age and younger. Tinea pedis is an uncommon pediatric disease in prepubescent children. Published data on the incidence of tinea pedis in pediatric patients indicates that the incidence of tinea pedis increases with age. O'Grady and Sahn have reported that the incidence in 100 subjects (mean age 5.6 years) was 1.3%, while other authors have reported incidences ranging from 2.2% (ages 7 to 10 years) to 8.2% (ages 11 to 14 years). More recently, Hapcioglu et al. have reported the prevalence of tinea pedis in 5,090 young children (<11 years) was 0.98%, with the incidence increasing to 2.9% in 2,068 older children (>11years).

3. Because tinea pedis is rare in children ages 0 to 11, conducting pediatric studies in this subpopulation would be highly impractical and would unnecessarily delay the approval of this product for the adult population and the pediatric population aged 12-18 years.

The applicant 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 and included subjects 12 years of age and older in phase 3 studies.

The division concurred with the applicant's assessment and recommended to Pediatric Review Committee (PeRC) that the partial waiver in pediatric patients birth to 11 years 11 months of age be granted (b) (4)

The Pediatric Review Committee (PeRC) discussed the waiver proposal on May 29, 2013. The PeRC agrees with the partial waiver in pediatric patients birth to less than 12 years of age because studies are impossible or highly impracticable and recommends

changing the reason for the waiver [redacted] (b) (4) to the studies are impossible or highly impracticable.

The committee also discussed the pediatric studies conducted in adolescents aged 12-17 years. The PeRC agrees with the Division's assessment based on 2 pivotal studies conducted which included pediatric subjects, pediatric PK studies and prior use of econazole nitrate cream in a similar population that the data supports the indication for ages 12 and older.

Comment: This reviewer has no objection to changing the justification of the waiver to "studies are impossible or highly impracticable".

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is minimal risk of overdose or abuse for Econazole Nitrate Foam 1%. Available data from the trials did not demonstrate a risk.

7.7 Additional Submissions / Safety Issues

The 120 day safety update was submitted on May 2, 2013. Per applicant "There are no available data to indicate any new or unexpected outcomes, safety findings, or concerns for Econazole Nitrate Foam, 1% that were not previously reported in NDA 205-175."

8 Postmarket Experience

Econazole Nitrate Foam, 1% is currently not marketed in any country.

9 Appendices

9.1 Literature Review/References

1. Dodds Ashley ES et al. Pharmacology of systemic antifungal agents. *Clin Infect Dis.* 2006(S01): S28-S39.
2. Lang PG and LeClercq AH. Increase in anticoagulant effect of warfarin in a patient using econazole cream. *J. Amer Acad Dermatol.* 2006(55): S117-S119.
3. Aria N and Kauffman CL. Important drug interactions and reactions in dermatology. *Dermatol Clin*. 2003(21) 207-215.
4. Weinstein A and Berman B. Topical treatment of common superficial tinea infections. *American Family Physician* 2002;65(10): 2095-2102

9.2 Labeling Recommendations

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 OPDP and DMPP consultative reviews. DMEPA finds the proposed proprietary name of "Ecoza" acceptable from a safety and promotional perspective. The review team had no objections to the proposed name Ecoza.

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 review. Proposed labeling is attached (section 9.3). Sections requiring additional discussion are presented below with comment:

- Indication: Ecoza (econazole nitrate) topical foam, 1%, is indicated for the treatment of interdigital tinea pedis caused by *Trichophyton rubrum, Trichophyton mentagrophytes,* and *Epidermophyton floccosum* in patients 12 years of age and older.

  Comment: The applicant's proposed labeling was revised to reflect the organisms commonly associated with the indication and in which at least some subjects have been evaluated.

- Contraindication: none

  Comment: No cases of hypersensitivity were identified in the studies. It is no longer recommended to routinely label for hypersensitivity unless there is evidence of a reaction.

  Warnings and precautions: 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.

Comment: The team concurred with the applicant's proposal to label for flammability in warnings and precautions. The language was slightly modified (b) (4) *" to "avoid heat, flame and smoking". It is this reviewer's opinion that this best captures risk and that* (b) (4) *" are redundant. Both versions appear in FDA labeling.*

- Adverse reactions

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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.

Comment: Few adverse reactions occurred in the clinical trials. Application site reactions were seen in both active and vehicle foam arms. This reviewer has recommended combining these reactions for labeling as reactions may be due to excipient present in the vehicle.

Drug-drug interactions*: Concomitant administration of econazole and warfarin has resulted in enhancement of anticoagulant effect. Most cases reported product application with use under occlusion, genital application, or application to a large body surface area which may increase the systemic absorption of econazole nitrate. Monitoring of International Normalized Ratio (INR) and/or prothrombin time may be indicated especially for patients who apply econazole to large body surface areas, in the genital area, or under occlusion.*

Comment: The Agency Division of Pharmacovigilance (DPV) evaluated the case reports describing drug-drug interactions with the use of topical econazole nitrate cream use and warfarin and recommends including language in all econazole labels regarding drug-drug interaction with warfarin. This reviewer is recommending similar labeling changes regarding drug-drug interactions with warfarin are included as class labeling in the econazole nitrate foam product's label.

- Pediatric use: Of the 173 subjects treated with Ecoza topical foam, 1% in the clinical studies, 2 subjects were 12-17 years old.

  In a pediatric maximal use trial, Ecoza topical foam, 1% was applied once daily to 18 eighteen subjects (aged 12 to 17 years) with interdigital tinea pedis for 28 days [see Clinical Pharmacology (12.3)]. The safety findings for patients 12 to 17 years were similar to those in adult population.

  Comment: Efficacy for use in the pediatric population was extrapolated. Safety is based on limited clinical trial data and the long history of topical Econazole Nitrate Cream. The review team recommends including the pediatric data generated from the clinical development program in this section.

- Microbiology: Econazole nitrate has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections [see Indications and Usage (1)].

  Epidermophyton floccosum
  Trichophyton mentagrophytes
  Trichophyton rubrum

  Comment: The applicant's proposed labeling was revised to reflect the organisms commonly associated with the indication and in which at least some subjects have been evaluated.

- Clinical studies: Table 1, (b) (4) presented efficacy outcome.

  Comment: Revisions to tables were made to simplify presentation of efficacy data to improve readability.

- Patient Information
  - Inform patients that Ecoza (econazole nitrate) topical foam, 1% is for topical use only. Ecoza (econazole nitrate) topical foam, 1% is not intended for oral, intravaginal, or ophthalmic use.
  - Ecoza topical foam, 1% is flammable; avoid heat, flame, and smoking during and immediately following application.
  - If a reaction suggesting sensitivity or chemical irritation develops with the use of Ecoza topical foam, 1%, use of the medication should be discontinued.

  Comment: Revisions to patient information to be conveyed by physician were made to highlight only the most significant information.

- Patient Information and Information for Use

Comment: Patient information was separated into 2 sections (PI and IFU) based on recommendations from DMPP. With a goal of making patient labeling more concise and eliminating redundancy, DDMP is implementing new recommendations for new products. This reviewer agrees with the goal of making patient labeling more concise.

9.2 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 the DODAC 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.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

AMY S WOITACH
09/20/2013

DAVID L KETTL
09/20/2013
Concur with approval recommendation. See CDTL review.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205-175 **Applicant:** AmDerma Pharmaceuticals, LLC **Stamp Date:** December 24, 2012

Drug Name: Econazole Nitrate Foam, 1% **NDA Type:** S

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1:A Multi-Center, Randomized, Double-Blind, Vehicle Controlled, Parallel Group Comparison	X			Two pivotal safety and efficacy studies appear adequate for review. Study #2 (303) includes 1% econazole

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study of the Safety and Efficacy of Econazole Nitrate Foam 1% and Foam Vehicle in Subjects with Interdigital Tinea Pedis Indication:interdigital tinea pedis Pivotal Study #2: A Multi-center, Randomized, Double-blind, Vehicle-controlled, Parallel Group Comparison of Econazole Nitrate Foam 1% vs Foam Vehicle and an Evaluator-blinded Comparison of Econazole Nitrate Foam 1% and Econazole Nitrate Cream 1% in Subjects with Interdigital Tinea Pedis Indication: interdigital tinea pedis				cream arm (and cream vehicle arm) to support safety bridge from the approved, referenced 1% cream to the newly proposed 1% foam, as the pk absorption is higher in the foam. No significant safety differences were observed by the applicant.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Study 302 was conducted in the U.S. and Dominican Republic (44/165 subjects in the MITT population were foreign). This will be a review issue. Study 303 was conducted exclusively in the U.S. (MITT population 256 subjects)
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			No TQT study was conducted, though econazole cream was originally approved in 1982, with no known CV safety issues. A proposal for a TQT waiver was submitted and reviewed in 2009.
20.	Has the applicant presented a safety assessment based on all	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			Studies 302 and 303: System Organ Class and Preferred Term map to MedDRA dictionary (Version 14.0) Study 207: SOC and PT coded using MedDRA Version 9.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A; Application is fileable from a clinical perspective

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

None

Reviewing Medical Officer Date

Clinical Team Leader Date

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

APPEARS THIS WAY ON ORIGINAL

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

/s/

AMY S WOITACH
02/12/2013

DAVID L KETTL
02/12/2013