CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-930

MEDICAL REVIEW

Deputy Division Director Memorandum

Application Type	NDA
Submission Number	21-930
Submission Code	N-000
Letter Date	May 4, 2005
Memorandum	November 9, 2005
Established Name	Fluocinolone acetonide oil, 0.01%
Therapeutic Class	Topical Corticosteroid
Applicant	Hill Dermaceuticals, Inc. 2650 South Mellonville Avenue Sanford, FL 32773-9311 (407) 323-1887

This memorandum is to correct some typographical errors found in previous reviews and submissions.

1. The correct concentration of the product is 0.01%. This is the same concentration used in the currently marketed product and all clinical studies.
2. The amount of drug packaged is not one ounce. The final product configuration are vials each filled with 4 mL.
3. The application may more properly classified as a 505(b)(2) application, as opposed to a 505(b)(1) application. For the purposes of User Fees, the application has been classified as an old (pre-1993) 505(b)(2). While the data to support the new indication listed in NDA 21-930 was generated by the applicant, NDA 21-930 is actually a supplement to NDA 19-452. NDA 21-930 is an administratively created NDA. NDA 19-452 was originally submitted as a 505(j) application referencing the agency's conclusions from the DESI review. The original fluocinolone acetonide product included in the DESI review was Synalar, NDA 12-787.
4. The applicant has chosen to use the established name in the submitted labeling due to the potential conflict with the name [redacted]. To distinguish this packaging configuration from the larger volume products, the name is listed as Fluocinolone acetonide oil, 0.01% ear drops. The carton and container labeling will need to be revised to be in conformance with the new package insert. This has been accepted by the applicant and is included in the action letter.

NDA 21-930 is recommended for approval for the treatment of chronic eczematous external otitis.

Wiley A. Chambers, MD
Deputy Division Director, DAIOP

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/s/

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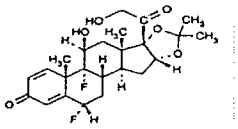
11/9/2005 05:01:32 PM
MEDICAL OFFICER

Janice Soreth
11/9/2005 05:07:55 PM
MEDICAL OFFICER

Clinical Labeling Review

Application Type	NDA
Submission Number	21-930
Submission Code	N-000
Letter Date	November 4, 2005
PDUFA Goal Date	November 9, 2005
Reviewer Name	Wiley A. Chambers, MD
Review Completion Date	November 7, 2005
Established Name	Fluocinolone acetonide solution, 0.1%
Proposed Trade Name	[redacted]
Therapeutic Class	Topical Corticosteroid
Applicant	Hill Dermaceuticals, Inc. 2650 South Mellonville Avenue Sanford, FL 32773-9311 (407) 323-1887
Priority Designation	P
Structure	
Dosing Regimen	Apply 5 drops into the affected ear, twice daily for one week
Indication	Chronic eczematous external otitis
Intended Population	Patients two years of age and older with chronic eczematous external otitis

Submitted: Revised Labeling

Reviewer's Comments: *Reviewer recommendations have been added to the text below.*

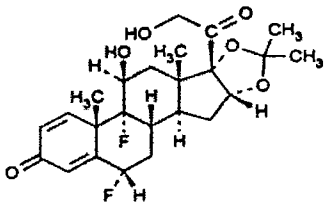
[redacted] (fluocinolone acetonide oil) 0.01% Ear Drops

For Otic Use Only-
Not for Ophthalmic Use

NDC 28105-160-12

DESCRIPTION

[redacted] contains fluocinolone acetonide {(6α, 11β, 16α)-6,9-difluoro-11,21-dihydroxy-16,17[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione, cyclic 16,17 acetal with acetone}, a synthetic corticosteroid. This formulation is also marketed as DermaSmoothe/FS Body Oil for the treatment of atopic dermatitis and DermaSmooth/FS Scale Oil for the treatment of psoriasis of the scalp. Chemically, fluocinolone acetonide is C_{24} H_{30} F_2 O_6. It has the following structural formula:



Fluocinolone acetonide in [redacted] has a molecular weight of 452.50. It is a white crystalline powder that is odorless, stable in light, and melts at 270°C with decomposition; soluble in alcohol, acetone and methanol; slightly soluble in chloroform; insoluble in water.

Each gram of [redacted] contains approximately 0.11 mg of fluocinolone acetonide in a blend of oils, which contains isopropyl alcohol, isopropyl myristate, light mineral oil, oleth-2, refined peanut oil NF and fragrances.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, fluocinolone acetonide has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusion of topical corticosteroids can enhance penetration. Topical corticosteroids can be absorbed from normal intact skin. Also, inflammation and/or other disease processes in the skin can increase percutaneous absorption.

[redacted] is in the low to medium range of potency as compared with other topical corticosteroids.

CLINICAL STUDIES

Efficacy in a placebo-controlled study for the treatment of chronic eczematous external otitis on 154 patients (adults and children 2 years of age and older) treated with five drops per ear of [redacted] twice daily, after 7 days of treatment, showed [redacted] to be superior to placebo in clearing the signs and symptoms of eczematous external otitis.

Clinical safety studies were conducted on the same formulation of fluocinolone acetonide oil 0.01%, marketed as Derma-Smoothe/FS Oil. Open-label safety studies on 33 children (20 subjects ages 2 to 6 years, 13 subjects ages 7 to 12 years) with moderate to severe stable atopic dermatitis, and baseline body surface area involvement greater than 75% in 18 patients, and 50% to 75% in 15 patients, were treated with Derma-Smoothe/FS Oil twice daily for 4 weeks. Morning pre-stimulation cortisol level and post-Cortrosyn stimulation cortisol level were obtained in each subject at the beginning of the trial and at the end of 4 weeks of treatment. At the end of treatment, 4 out of 18 subjects aged 2 to 5 years showed low pre-stimulation cortisol levels (3.2 to 6.6 μg/dL; normal: cortisol > 7μg/dL) but all had normal responses to 0.25 mg of Cortrosyn stimulation (cortisol > 18 μg/dL).

A clinical study was conducted to assess the safety of Derma-Smoothe/FS Oil, which contains refined peanut oil, on subjects with known peanut allergies. The study enrolled 13 patients with atopic dermatitis, 6 to 17 years of age. Of the 13 patients, 9 were Radioallergosorbent Test (RAST) positive to peanuts and 4 had no peanut sensitivity (controls). The study evaluated the responses to both prick test and patch test utilizing peanut oil NF, Derma-Smoothe/FS® Oil and histamine/saline controls on the 13 individuals . These subjects were also treated with Derma-Smoothe/FS Oil twice daily for 7 days. Prick test and patch test results for all 13 patients were negative to Derma-Smoothe/FS Oil and the refined peanut oil. One of the 9 peanut-sensitive patients experienced an exacerbation of atopic dermatitis after 5 days of Derma-Smoothe/FS Oil. Importantly, the bulk peanut oil NF, used in Derma-Smoothe/FS Oil is heated at 475° F for at least 15 minutes, which should provide for adequate decomposition of allergenic proteins.

INDICATION AND USAGE

[redacted] is a low to medium potency corticosteroid indicated for the treatment of chronic eczematous external otitis in adults and pediatric patients 2 years old and older.

CONTRAINDICATIONS

[redacted] is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

This product contains refined peanut oil NF (See PRECAUTIONS).

PRECAUTIONS

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Infrequently, signs and symptoms of glucocorticoid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See PRECAUTIONS-Pediatric use)

Allergic contact dermatitis to any component of topical corticosteroids is usually diagnosed by a failure to heal rather than noting a clinical exacerbation, which may occur with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic testing. One peanut-sensitive child experienced a flare of his atopic dermatitis after 5 days of twice daily treatment with Derma-Smoothe/FS Oil (see CLINICAL STUDIES section).

If wheal and flare type reactions (which may be limited to pruritus) or other manifestations of hypersensitivity develop, DermOtic™ Oil should be discontinued immediately and appropriate therapy instituted.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of [redacted] should be discontinued until the infection has been adequately controlled.

[redacted] is formulated with 48% refined peanut oil NF. Peanut oil used in this product is routinely tested for peanut proteins using a sandwich enzyme-linked immunosorbent assay test (S-ELISA) kit, which can detect peanut proteins to as low as 2.5 parts per million (ppm). Physicians should use caution in prescribing [redacted] for peanut-sensitive individuals.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external ear use only. Do not use occlusive dressings.

2. Avoid contact with the eyes. In case of contact, wash eyes liberally with water.

3. This medication should not be used for any disorder other than that for which it was prescribed.

4. Patients should promptly report to their physician any worsening of their skin condition.

5. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests: The following tests may be helpful in evaluating patients for HPA axis suppression:
ACTH stimulation test
A.M. plasma cortisol test
Urinary free cortisol test

Carcinogenesis, mutagenesis, and impairment of fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of [redacted] Studies have not been performed to evaluate the mutagenic potential of fluocinolone acetonide, the active ingredient in [redacted]™ Some corticosteroids have been found to be genotoxic in various genotoxicity tests (i.e. the in vitro human peripheral blood lymphocyte chromosome aberration assay with metabolic activation, the in vivo mouse bone marrow micronucleus assay, the Chinese hamster micronucleus test and the in vitro mouse lymphoma gene mutation assay).

Pregnancy: Teratogenic effects: Pregnancy category C: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

There are no adequate and well-controlled studies in pregnant women on teratogenic effects from [redacted]™ Therefore, [redacted]™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when [redacted] is administered to a nursing woman.

Pediatric Use: [redacted] may be used twice daily for up to 2 weeks in pediatric patients 2 years of age and older with chronic eczematous external otitis.

[redacted] is not recommended for use on the face (See ADVERSE REACTIONS section).

Because of a higher ratio of skin surface area to body mass, children are at a greater risk than adults of HPA-axis-suppression when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children. (See PRECAUTIONS).

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

[redacted] is formulated with 48% refined peanut oil NF, in which peanut protein is not detectable at 2.5 ppm. Physicians should use caution in prescribing [redacted] for peanut sensitive individuals. [redacted]

ADVERSE REACTIONS

The following local adverse reactions have been reported infrequently with topical corticosteroids. They may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria. One peanut sensitive child experienced a flare of his atopic dermatitis after 5 days of twice daily treatment with Derma-Smoothe/FS Oil.

OVERDOSAGE

Topically applied [redacted] can be absorbed in sufficient amounts to produce systemic effects (See PRECAUTIONS).

DOSAGE AND ADMINISTRATION

For the treatment of chronic eczematous external otitis, using the supplied ear-dropper, apply 5 drops of [redacted] into the affected ear. To apply, tilt head to one side so that the ear is facing up. Then gently pull the ear lobe backward and upward and apply 5 drops of [redacted] into the ear. Keep head tilted for about a minute to allow [redacted] to penetrate lower into the ear canal. Gently pat excess material dripping out of the ear using a clean cotton ball. Follow these instructions twice each day for 7 to 14 days.

HOW SUPPLIED

[redacted] fluocinolone acetonide oil) 0.01% Ear Drops is supplied as a pack of 3 vials, each containing 4 mL, for a total of 12 mL net weight (Droppers Included) (NDC # 28105-160-12).

Keep tightly closed. Store at 20°-25° C (68° to 77° F); excursions permitted to 15°-30° C (59°-86°F.) [see USP Controlled Room Temperature]

CAUTION: Rx only

MANUFACTURED AND DISTRIBUTED BY:
Hill Dermaceuticals, Inc.
Sanford, Florida 32773

Rev. CODE xxxxx
Date: 11/05

1 Page(s) Withheld

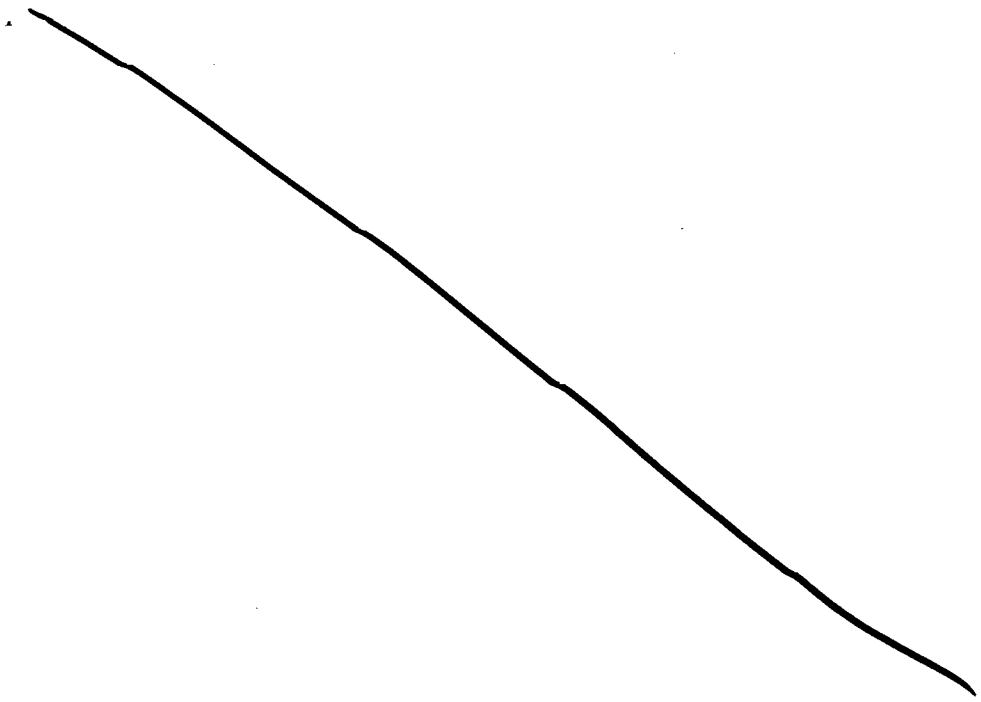
_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

Recommendations:
Pending comments from DMETS on the new proposed trademark, it is recommended that the labeling be revised as identified in this review. In addition, the following changes should be made to the DermaSmoothe oil products as requested by the Division of Dermatology and Dental Products:



Wiley A. Chambers, MD

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/s/

Wiley Chambers
11/8/2005 11:16:52 AM
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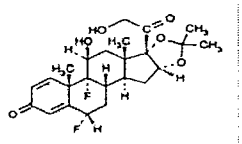
Janice Soreth
11/8/2005 01:09:45 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-930
Submission Code	N-000
Letter Date	May 4, 2005
Stamp Date	May 9, 2005
PDUFA Goal Date	November 9, 2005
Reviewer Name	Wiley A. Chambers, MD
Review Completion Date	November 4, 2005
Established Name	Fluocinolone acetonide solution, 0.1%
Proposed Trade Name	[redacted]
Therapeutic Class	Topical Corticosteroid
Applicant	Hill Dermaceuticals, Inc. 2650 South Mellonville Avenue Sanford, FL 32773-9311 (407) 323-1887
Priority Designation	P
Structure	
Dosing Regimen	Apply 5 drops into the affected ear, twice daily for one week
Indication	Chronic eczematous external otitis
Intended Population	Patients two years of age and older with chronic eczematous external otitis

Reviewer's Comments: *Comments by the Reviewer are in italics.*

Table of Contents

1.1 RECOMMENDATION ON REGULATORY ACTION 4
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS 4
1.2.1 Risk Management Activity 4
1.2.2 Required Phase 4 Commitments 4
1.2.3 Other Phase 4 Requests 4
1.3 SUMMARY OF CLINICAL FINDINGS 4
1.3.1 Brief Overview of Clinical Program 4
1.3.2 Efficacy 5
1.3.3 Safety 5
1.3.4 Dosing Regimen and Administration 5
1.3.5 Drug-Drug Interactions 5
1.3.6 Special Populations 5
2 INTRODUCTION AND BACKGROUND 5
2.1 PRODUCT INFORMATION 5
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS 6
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 6
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 6
2.5 PRESUBMISSION REGULATORY ACTIVITY 6
2.6 OTHER RELEVANT BACKGROUND INFORMATION 6
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 6
3.1 CMC AND PRODUCT MICROBIOLOGY 6
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY 6
4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 7
4.1 SOURCES OF CLINICAL DATA 7
4.2 TABLES OF CLINICAL STUDIES 7
4.3 REVIEW STRATEGY 7
4.4 DATA QUALITY AND INTEGRITY 7
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES 7
4.6 FINANCIAL DISCLOSURES 7
5 CLINICAL PHARMACOLOGY 7
5.1 PHARMACOKINETICS 7
5.2 PHARMACODYNAMICS 8
5.3 EXPOSURE-RESPONSE RELATIONSHIPS 8
6 INTEGRATED REVIEW OF EFFICACY 8
6.1 INDICATION 8
6.1.1 Methods 8
6.1.2 General Discussion of Endpoints 8
6.1.3 Study Design 8
6.1.4 Efficacy Findings 10
6.1.5 Clinical Microbiology 13
6.1.6 Efficacy Conclusions 13
7 INTEGRATED REVIEW OF SAFETY 13
7.1 METHODS AND FINDINGS 13
7.1.1 Deaths 13
7.1.2 Other Serious Adverse Events 13
7.1.3 Dropouts and Other Significant Adverse Events 13

7.1.4 Other Search Strategies 14
7.1.5 Common Adverse Events 14
7.1.6 Less Common Adverse Events 15
7.1.7 Laboratory Findings 15
7.1.8 Vital Signs 16
7.1.9 Electrocardiograms (ECGs) 16
7.1.10 Immunogenicity 17
7.1.11 Human Carcinogenicity 17
7.1.12 Special Safety Studies 17
7.1.13 Withdrawal Phenomena and/or Abuse Potential 17
7.1.14 Human Reproduction and Pregnancy Data 17
7.1.15 Assessment of Effect on Growth 17
7.1.16 Overdose Experience 17
7.1.17 Postmarketing Experience 17
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 18
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 18
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety 18
7.2.3 Adequacy of Overall Clinical Experience 19
7.2.4 Adequacy of Special Animal and/or In Vitro Testing 19
7.2.5 Adequacy of Routine Clinical Testing 19
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup 19
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study 19
7.2.8 Assessment of Quality and Completeness of Data 19
7.2.9 Additional Submissions, Including Safety Update 19
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS 20
7.4 GENERAL METHODOLOGY 20
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence 20
7.4.2 Explorations for Predictive Factors 20
7.4.3 Causality Determination 21

8 ADDITIONAL CLINICAL ISSUES 21

8.1 DOSING REGIMEN AND ADMINISTRATION 21
8.2 DRUG-DRUG INTERACTIONS 21
8.3 SPECIAL POPULATIONS 21
8.4 PEDIATRICS 21
8.5 ADVISORY COMMITTEE MEETING 21
8.6 LITERATURE REVIEW 21
8.7 POSTMARKETING RISK MANAGEMENT PLAN 21
8.8 OTHER RELEVANT MATERIALS 21

9 OVERALL ASSESSMENT 22

9.1 CONCLUSIONS 22
9.2 RECOMMENDATION ON REGULATORY ACTION 22
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS 22
9.3.1 Risk Management Activity 22
9.3.2 Required Phase 4 Commitments 22
9.3.3 Other Phase 4 Requests 22
9.4 LABELING REVIEW 22
9.5 COMMENTS TO APPLICANT 28

Executive Summary

1.1 Recommendation on Regulatory Action

NDA 21-790 is recommended to be approved from a clinical prospective with labeling revisions identified in this review.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Routine reporting of adverse events is recommended for this application. No additional postmarketing risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No Phase 4 clinical studies are recommended for this application.

1.2.3 Other Phase 4 Requests

No additional Phase 4 requests are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The submitted application is an efficacy supplement to NDA 19-452, Derma-Smoothe/FS Topical Oil. NDA 19-452 was approved after review by the Division of Dermatologic and Dental Products. The supplement has been administratively converted to NDA 21-790 because the clinical expertise for the review of this indication is located in the Division of Anti-Infective and Ophthalmology Products. There are no changes in the manufacturing and controls section of this application with the exception of the packaging size which has been reduced from four ounces to one ounce in this application.

[redacted] (fluocinolone acetonide oil) 0.1% is a low to medium range potency corticosteroid for topical administration to the external ear canal in patients age 2 years and greater with chronic eczematous external otitis. Two clinical studies were conducted in patients aged 2-85 years old.

1.3.2 Efficacy

Two new studies using an identical protocol have been conducted in a total of 151 patients, randomized equally between active treatment and mineral oil as placebo. There are a limited number of patients (approximately 30%) with complete clearing, but treatment is significantly more effective than placebo (approximately 5% complete clearing). The findings are consistent between all investigators, across studies, and among most of the signs and symptoms.

1.3.3 Safety

No new findings related to safety have been identified in these studies. The safety database in this submission is small; however, combined with the NDA 19-452, the database is adequate.

1.3.4 Dosing Regimen and Administration

Five drops of [redacted] are administered to the external ear canal twice daily for one week.

1.3.5 Drug-Drug Interactions

No known drug interactions.

1.3.6 Special Populations

No special populations have been identified or studied.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

[redacted] are 0.1% fluocinolone acetonide oil formulations approved for atopic dermatitis and psoriasis of the scalp. [redacted] (fluocinolone acetonide oil) 0.1% is a low to medium range potency corticosteroid for topical administration to the external ear canal in patients age 2 years and greater with chronic eczematous external otitis. It is the same formulation as the Topical Oil and Scalp Oil. The submitted application requests this additional indication.

2.2 Currently Available Treatment for Indications

There are currently no approved new drug applications for the proposed indication.

2.3 Availability of Proposed Active Ingredient in the United States

Fluocinolone is currently approved in multiple different dosage forms. Fluocinolone has the same safety profile as other low to medium range potency corticosteroids.

2.4 Important Issues With Pharmacologically Related Products

Corticosteroids have a known safety and efficacy profile. Fluocinolone demonstrates properties that are consistent with other corticosteroids.

2.5 Presubmission Regulatory Activity

No significant pre-regulatory activities.

2.6 Other Relevant Background Information

No significant other information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC and Product Microbiology

The submitted application is an efficacy supplement to NDA 19-452, Derma-Smoothe/FS Topical Oil. There are no changes in the manufacturing and controls section of this application with the exception of the packaging size which has been reduced from four ounces to one ounce in this application.

3.2 Animal Pharmacology/Toxicology

The submitted application is an efficacy supplement to NDA 19-452, Derma-Smoothe/FS Topical Oil. There are no additional non-clinical studies submitted to this application.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The submitted clinical trials, submitted published articles and a Medline literature search have been considered for the review of this application.

4.2 Tables of Clinical Studies

Protocol 31 A & B were conducted using identical protocols in a total of 75 patients treated with the fluocinolone and 79 patients treated with placebo (mineral oil).

4.3 Review Strategy

There is a long history of fluocinolone use in a variety of different dosage forms and indications. No significant new information was identified in the literature review. The submitted studies form the basis for the new indication requested in this application. The entire application was reviewed by this reviewer.

4.4 Data Quality and Integrity

DSI audits have been conducted for some of the investigators in the clinical studies. Other investigators used in these studies have been recently inspected due to their involvement in other applications. No significant issues were identified in the audits.

4.5 Compliance with Good Clinical Practices

There is no evidence to believe that the trials were not conducted in accordance with good clinical practices and acceptable ethical standards.

4.6 Financial Disclosures

Financial disclosure forms were submitted. No issues have been identified with respect to financial interests or data integrity.

5 CLINICAL PHARMACOLOGY

The submitted application is an efficacy supplement to NDA 19-452, Derma-Smoothe/FS Topical Oil. There are no additional biopharmacology studies submitted to this application.

5.1 Pharmacokinetics

No new information submitted. See NDA 19-452.

5.2 Pharmacodynamics

No new information submitted. See NDA 19-452.

5.3 Exposure-Response Relationships

No new information submitted. See NDA 19-452.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is for the treatment of chronic eczematous external otitis.

6.1.1 Methods

Studies 31 A&B were reviewed to support the indication.

6.1.2 General Discussion of Endpoints

The primary endpoint was the proportion of patients with a score of 0 at Day 7 for erythema, scaling, erosion, debris and pruritus. During the development of this indication, the Agency indicated that successful treatment would be considered only if all 5 signs and symptoms had a score of zero (as opposed to any single score). If individual scores were to be accepted, corrections for the multiple endpoints would have to be made. The applicant did not correct the protocol and did not correct for the potential multiple comparisons with 5 different signs and symptoms. This review maintains the Agency's prior position that successful treatment is clearing of all 5 signs and symptoms. The secondary endpoints included physician and patient global scores and improvement from baseline.

6.1.3 Study Design

Studies 31 A&B were controlled, phase 3, multi-center, randomized, double-blinded, placebo-controlled, parallel study for the first 7 days, followed by a cross-over (of all patients with inadequate responses) to open-label active treatment for the next 7 days. Specific inclusion/exclusion criteria include: healthy male and female patients 2 years and older, with moderate to severe chronic eczematous external otitis.

Study Flow Chart

Procedures	Day -7 Screen*	Day 0 Baseline*	Day 7	Day 14	Day 28 Post-treatment
Visit Window:	-	*± 2 days*	*± 2 days*	*± 2 days*	
Informed Consent / Assent	X				
Demographics and History	X				
Inclusion/Exclusion	X	X			
Enroll in Study (issue patient number)		X			
Pregnancy Test**		X			
Investigator					
Global Severity	X	X	X	X	X
Grade Signs/Symptoms		X	X	X	X
Patient Assessment of Pruritus		X	X	X	X
Patient Assessment of Improvement			X	X	X
Audiology (voluntary)		X			X
Safety Evaluation					
Adverse Events			X	X	X
Photographs (voluntary)		X	X	X	
Dispense Test Product		X	X		
Collect Test Product			X	X	
Record missed doses			X	X	
Concomitant/Concurrent Medications		X	X	X	X

* The screening and baseline visit may be the same day if no wash out of other medications is required.
** Pregnancy test required for females who have started menstruating.

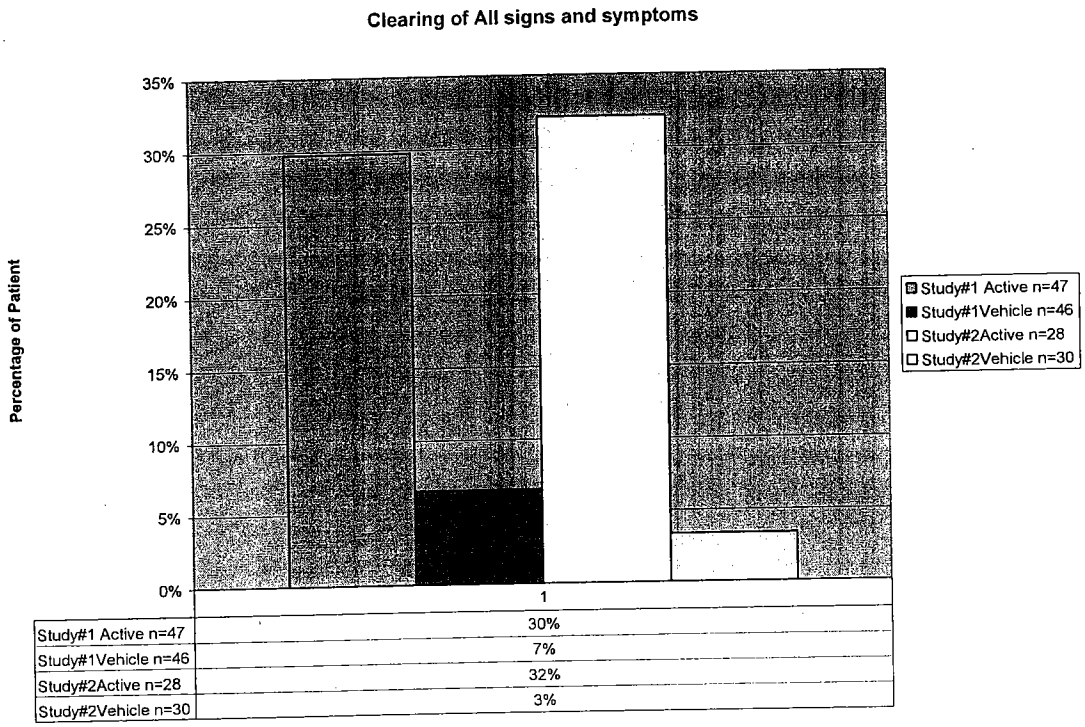
Reviewer's Comments: *For the purposes of this review, evaluations of efficacy were stopped at Day 7 prior to the open label portion. Evaluations of safety were reviewed through the entire 28 day period of the study.*

Investigators:

1. Bradley Reese, M.D., Florida Otolaryngology Group, P.A. 5979 Vineland Road, Suite 101 Orlando, Florida 32819
2. Stella Calobrisi, M.D., The Galen Medical Building, 880 Northwest 13th Street, Suite 3B Boca Raton, Florida 33486
3. Anthony Magit, M.D., Children's Hospital, San Diego 3030 Children's Way, MC 5024 San Diego, California 92123
4. Juan Bonilla, M.D., 525 Oak Center Drive, Suite 400 San Antonio, Texas 78258
5. Jack Anon, M.D., ENT Specialists of NW PA C/O Square One, 3256 W. 26th Street, Erie, Pennsylvania 16506

Reviewer's Comments: *Investigators are considered qualified and represent different regions of the United States.*

6.1.4 Efficacy Findings



Reviewer's Comments: *The differences between groups in each study were statistically significant (p=0.003 for each study).*

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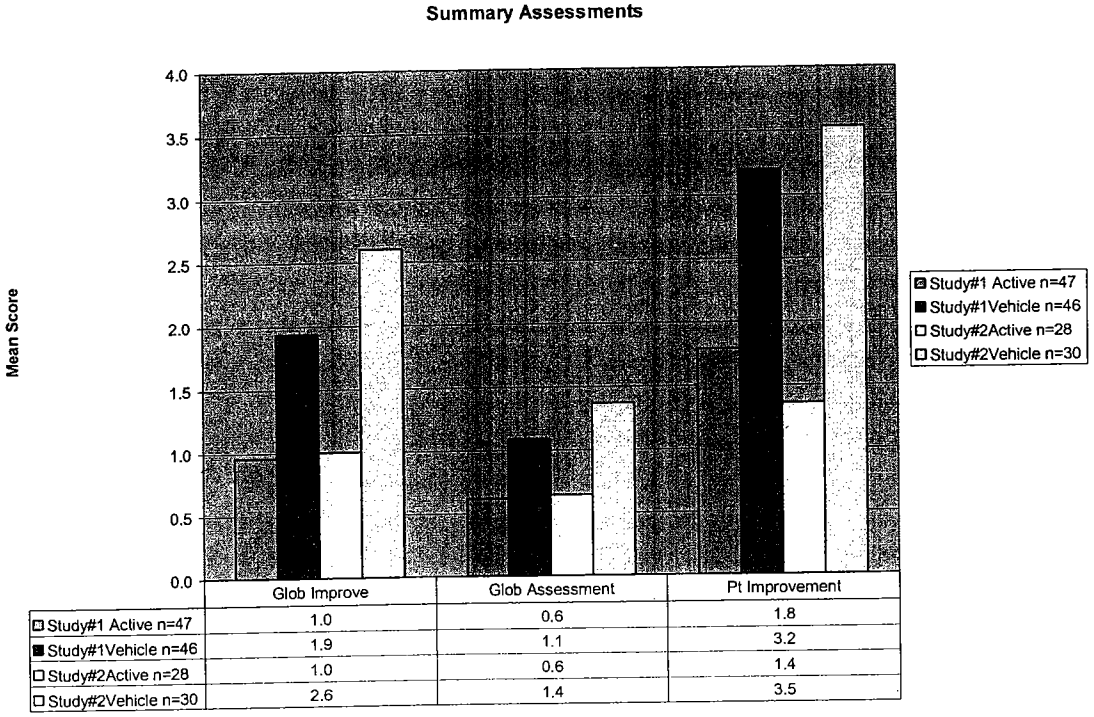

	Glob Improve	Glob Assessment	Pt Improvement
Study#1 Active n=47	1.0	0.6	1.8
Study#1Vehicle n=46	1.9	1.1	3.2
Study#2Active n=28	1.0	0.6	1.4
Study#2Vehicle n=30	2.6	1.4	3.5

Reviewer's Comments: *All differences between active and vehicle are statistically significant ($p \leq 0.002$).*

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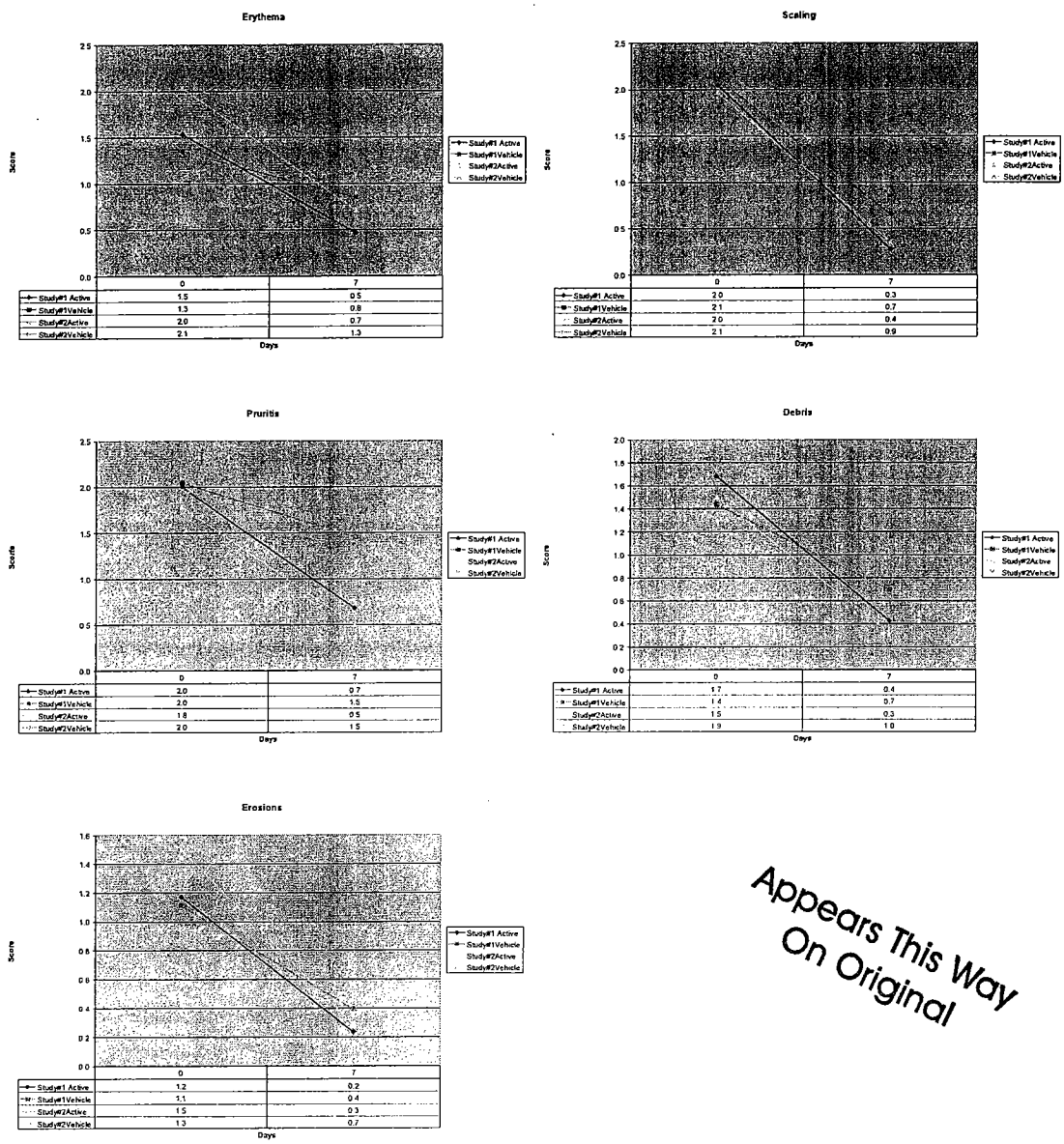
On Original

The findings are supported by individual signs and symptom differences listed below:



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Reviewer's Comments: *Statistically significant ($p \leq 0.015$) differences between groups were demonstrated for erythema, scaling and pruritis in both studies. A statistically significant difference ($p=0.003$) was demonstrated in only one study (#2) for debris. Statistically significant differences were not demonstrated for erosions.*

6.1.5 Clinical Microbiology

Not applicable. The product is not an antimicrobial product.

6.1.6 Efficacy Conclusions

While there are a limited number of successful patients (approximately 30%), treatment is significantly more effective than placebo (approximately 5%). The findings are consistent between all investigators, across studies, and among most of the signs and symptoms.

7 INTEGRATED REVIEW OF SAFETY

There are no significant new issues of safety identified in this review.

7.1 Methods and Findings

The new studies (31A&B) were reviewed together with the findings from the NDA 19-452.

7.1.1 Deaths

No deaths.

7.1.2 Other Serious Adverse Events

No serious adverse events.

7.1.3 Dropouts and Other Significant Adverse Events

Seven patients dropped out of the studies, six patients in the placebo arm and one patient in the fluocinolone arm (hypermania).

7.1.3.1 Overall profile of dropouts

Seven patients dropped out of the studies six patients in the placebo arm and one patient in the fluocinolone arm (hypermania).

7.1.3.2 Adverse events associated with dropouts

Seven patients dropped out of the studies six patients in the placebo arm and one patient in the fluocinolone arm (hypermania).

7.1.3.3 Other significant adverse events

None.

7.1.4 Other Search Strategies

The principal database for safety remains the NDA 19-452.

7.1.5 Common Adverse Events

With the exception of cough and headache, no adverse event was reported in 3 or more patients. Cough and headache were reported in 3 placebo patients each. Upper respiratory tract infections and eczematous otitis of the ear were reported in two patients on fluocinolone; no other adverse event term was reported in more than one patient. None of the events was serious.

7.1.5.1 Eliciting adverse events data in the development program

No special methods were used.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Actual terms were provided because so few events were reported.

7.1.5.3 Incidence of common adverse events

No adverse events were considered common.

7.1.5.4 Common adverse event tables

Investigat	ID	Group	Adverse Event	Event Start	Evenet End	Severity
Magit	10	Active	Acute Gastroenteritis (Intermittent)	01-16-03		Mod
Reese	179	Active	Bilateral Itching Eyes	04-17-03		Mild
Reese	183	Active	Burning Bilateral Ear Canals Upon Study Article Administration	05-07-03	05-07-03	Mod
Reese	183	Active	Burning Bilateral Ear Canals Upon Study Article Administration	05-08-03	05-08-03	Mod
Reese	193	Active	Eczematous Otitis L Ear	08-21-03		Mod
Reese	169	Active	Eczematous Otitis Right Ear	02-26-03		Mod
Reese	70	Active	Eczematous Otitis Right Ear	10-01-03		Mod
Magit	10	Active	Fever	01-11-03	01-11-03	Mild
Anon	113	Active	Headache	05-05-03	05-05-03	Mild
Reese	73	Active	Hypermania	01-20-04	01-21-04	Mod
Magit	10	Active	Hypoglycemia	01-22-03	01-22-03	Mod
Anon	54	Active	Influenza	12-20-03	12-24-03	Mod
Magit	15	Active	L Otitis Externa	04-17-03	04-23-03	Mod
Anon	239	Active	Left Ear Fungal Infection	04-14-04		Mild
Reese	172	Active	Nausea	02-18-03	02-18-03	Mod
Reese	176	Active	Non-Insulin Dependent Diabetes Mellitus	04-07-03		Mild
Magit	12	Active	Preauricular Pain - Left	03-17-03	04-01-03	Mod
Reese	179	Active	Sinus Infection	05-01-03	05-07-03	Mild
Magit	18	Active	URI	11-17-03		Mild
Magit	23	Active	URI	08-15-04	08-17-04	Mild
Reese	172	Active	Vomiting X1	02-18-03	02-18-03	Mild
Anon	232	Active	Worsening Of Right Ear External Eczematous Otitis	03-02-04	03-18-04	Mod
Reese	186	Vehicle	Bilateral Burning Eyes	05-31-03	05-31-03	Sev
Reese	186	Vehicle	Bilateral Burning Eyes	06-01-03	06-01-03	Sev
Magit	114	Vehicle	Bilateral Ear Pain	04-14-03	04-14-03	Mod
Anon	112	Vehicle	Common Cold	04-21-03	05-02-03	Mild
Anon	112	Vehicle	Cough	04-28-03	05-07-03	Mod
Magit	21	Vehicle	Cough	04-26-04	05-02-04	Mod
Anon	62	Vehicle	Cough	02-09-04		Mild
Reese	71	Vehicle	Dizziness	12-11-03	12-11-03	Mod

Reese	71	Vehicle	Elevated Temperature	12-11-03	12-11-03	Mod
Magit	16	Vehicle	Fungal Otitis Left Ear	07-23-03	07-30-03	Mod
Reese	192	Vehicle	Hard Palate Abrasion	08-05-03		Mild
Anon	112	Vehicle	Headache	04-21-03	05-02-03	Mod
Reese	186	Vehicle	Headache	05-31-03	05-31-03	Mild
Reese	186	Vehicle	Headache	06-01-03	06-01-03	Mild
Magit	21	Vehicle	Headache	04-19-04	04-22-04	Mild
Reese	186	Vehicle	Metallic Taste In Throat	05-31-03	05-31-03	Mild
Reese	186	Vehicle	Metallic Taste In Throat	06-01-03	06-01-03	Mild Mild
Anon	122	Vehicle	Mild Erythema - Right Ear	07-17-03	07-23-03	Mild
Anon	234	Vehicle	Mild Lateral Left Neck Pain	03-15-04	03-20-04	Mild
Reese	186	Vehicle	Nausea	05-31-03	05-31-03	Mild
Reese	186	Vehicle	Nausea	06-01-03	06-01-03	Mold
Anon	103	Vehicle	Otitis Media Right Ear	03-27-03	04-08-03	Sev
Magit	29	Vehicle	Papular Rash Bilateral Ears	12-10-04		Mod
Anon	241	Vehicle	Right Acute Otitis Media	04-01-04	04-15-04	Self
Anon	241	Vehicle	Right Ear Myringitis	04-01-04	04-15-04	Mild
Anon	241	Vehicle	Right Tympanic Membrane Perforation	04-01-04	04-15-04	Mild
Reese	282	Vehicle	Sensorineural Hearing Loss Left Ear	07-19-04		Mod
Magit	11	Vehicle	Skin Infection	02-04-03	02-08-03	Mild
Anon	125	Vehicle	Small Amount Of Blood - Right Ear	08-10-03	08-10-03	Mild
Magit	19	Vehicle	Uri	11-20-03		Mild
Magit	5	Vehicle	Wheezing	10-20-02	10-20-02	Mod
Anon	234	Vehicle	Worsening Of Pre-Existing Intermittent Headaches	03-06-04	03-14-04	Mod

7.1.5.5 Identifying common and drug-related adverse events

No adverse events were considered common.

7.1.5.6 Additional analyses and explorations

No additional analyses were considered necessary.

7.1.6 Less Common Adverse Events

The corticosteroid class events are considered less common adverse events. See NDA 19-452.

7.1.7 Laboratory Findings

See NDA 19-452. No laboratories studies were conducted for these studies.

7.1.7.1 Overview of laboratory testing in the development program

See NDA 19-452. No laboratories studies were conducted for these studies.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See NDA 19-452. No laboratories studies were conducted for these studies.

7.1.7.3 Standard analyses and explorations of laboratory data

See NDA 19-452. No laboratories studies were conducted for these studies.

7.1.7.4 Additional analyses and explorations

See NDA 19-452. No laboratories studies were conducted for these studies.

7.1.7.5 Special assessments

See NDA 19-452. No laboratories studies were conducted for these studies.

7.1.8 Vital Signs

See NDA 19-452. No vitals signs were routinely monitored.

7.1.8.1 Overview of vital signs testing in the development program

See NDA 19-452. No laboratories studies were conducted for these studies.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See NDA 19-452. No laboratories studies were conducted for these studies.

7.1.8.3 Standard analyses and explorations of vital signs data

See NDA 19-452. No laboratories studies were conducted for these studies.

7.1.8.4 Additional analyses and explorations

See NDA 19-452. No laboratories studies were conducted for these studies.

7.1.9 Electrocardiograms (ECGs)

See NDA 19-452. No ECGs were conducted for these studies.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

See NDA 19-452. No ECGs were conducted for these studies.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See NDA 19-452. No ECGs were conducted for these studies.

7.1.9.3 Standard analyses and explorations of ECG data

See NDA 19-452. No ECGs were conducted for these studies.

7.1.9.4 Additional analyses and explorations

See NDA 19-452. No ECGs were conducted for these studies.

7.1.10 Immunogenicity

Fluocinolone, as well as other corticosteroids may block immunogenic responses.

7.1.11 Human Carcinogenicity

See NDA 19-452. No carcinogenicity studies were submitted with this application.

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Corticosteroids if administered for a long period of time must be tapered off to avoid rebounds of inflammation and if administered systemically, to allow normal endogenous steroid production to return. No unique issues have been raised in this submission.

7.1.14 Human Reproduction and Pregnancy Data

No new information in this submission. See NDA 19-452.

7.1.15 Assessment of Effect on Growth

No new information in this submission. See NDA 19-452.

7.1.16 Overdose Experience

No new information in this submission. See NDA 19-452.

7.1.17 Postmarketing Experience

No new information in this submission. See NDA 19-452.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

	Fluocinolone	Placebo
Gender	31♂ 44♀	31♂ 48♀
Age	2-85 years	4-85 years
Race	62 Caucasian 7 Black 2 Asian 4 Other	69 Caucasian 4 Black 2 Asian 5 Other

7.2.1.1 Study type and design/patient enumeration

See above.

7.2.1.2 Demographics

See above.

7.2.1.3 Extent of exposure (dose/duration)

All patients received the same dosing schedule. Five drops per application, 2 applications per day for seven days.

The following number of patients missed treatment doses:

Number of Missed Doses	Fluocinolone	Placebo
One dose	13 (17%)	19 (25%)
2-4 doses	2 (3%)	7 (9%)
>4 doses	1 (1%)	6 (8%)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

None.

7.2.2.1 Other studies

None.

7.2.2.2 Postmarketing experience

None.

7.2.2.3 Literature

A Medline search was conducted which did not yield any significant additional information except that fluocinolone acetonide has been shown in the past to be effective for chronic eczematous external otitis. The formulation studied does not appear to have been previously marketed.

7.2.3 Adequacy of Overall Clinical Experience

The submitted studies, in combination with the information submitted to NDA 19-452, is sufficient to support the safety and efficacy of fluocinolone acetonide in chronic eczematous external otitis.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There is no adequate nonclinical model for this disease. No special animal and/or in vitro testing was considered necessary.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing was considered adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See NDA 19-452. No additional studies were submitted.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The product labeling should include corticosteroid class labeling.

7.2.8 Assessment of Quality and Completeness of Data

Coupled with NDA 19-452, the information is adequate.

7.2.9 Additional Submissions, Including Safety Update

The safety update did not provide any significant new information.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

No new information in this submission. See NDA 19-452.

7.4 General Methodology

This application contained only two studies. The primary support for the drug product is found in NDA 19-452.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Study data between studies is very similar and can be combined.

7.4.1.1 Pooled data vs. individual study data

Study data between studies is very similar and can be combined.

7.4.1.2 Combining data

Study data between studies is very similar and can be combined.

7.4.2 Explorations for Predictive Factors

Not applicable. Only one dose was tested.

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable. Only one dose was tested.

7.4.2.2 Explorations for time dependency for adverse findings

Not applicable. Treatment was for a limited time frame.

7.4.2.3 Explorations for drug-demographic interactions

Not studied.

7.4.2.4 Explorations for drug-disease interactions

Not studied.

7.4.2.5 Explorations for drug-drug interactions

See NDA 19-452. Not studied in this application.

7.4.3 Causality Determination

No possible to determine.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Only one dose concentration, frequency and regimen was studied.

8.2 Drug-Drug Interactions

Not studied in this submission. See NDA 19-452.

8.3 Special Populations

There are no special considerations due to age, race or gender. Patients aged 2-85 were included in the study. No differences were observed based on age, race or gender.

8.4 Pediatrics

Pediatric patients were included in the clinical studies. No differences based on age were observed.

8.5 Advisory Committee Meeting

No advisory committee meeting was held for this application.

8.6 Literature Review

Studies of different formulations of this drug product have been performed dating back over 30 years. The conclusions concerning these trials are similar to the conclusions in these trials.

8.7 Postmarketing Risk Management Plan

No risk plan has been submitted or is considered needed.

8.8 Other Relevant Materials

No other submissions have been reviewed.

9 OVERALL ASSESSMENT

9.1 Conclusions

The submitted studies support the proposed indication for treatment of chronic eczematous external otitis.

9.2 Recommendation on Regulatory Action

NDA 21-930 is recommended for approval for the indication of treatment of chronic eczematous external otitis with the labeling revisions listed in this review.

9.3 Recommendation on Postmarketing Actions

There are no risk management activities or Phase 4 studies recommended for this application.

9.3.1 Risk Management Activity

There are no risk management activities or Phase 4 studies recommended for this application.

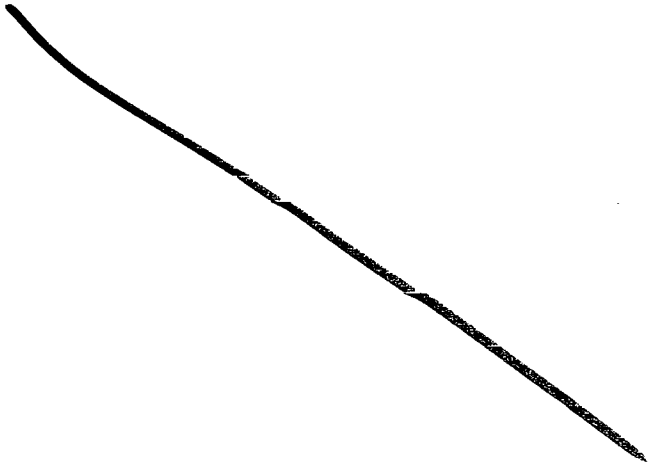
9.3.2 Required Phase 4 Commitments

There are no risk management activities or Phase 4 studies recommended for this application.

9.3.3 Other Phase 4 Requests

There are no risk management activities or Phase 4 studies recommended for this application.

9.4 Labeling Review



5 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2

Rev. CODE xxxxx
Date: 11/05

9.5 Comments to Applicant

It is recommended that the labeling be revised to match the draft labeling identified above.

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

/s/

Wiley Chambers
11/9/2005 09:36:27 AM
MEDICAL OFFICER

Janice Soreth
11/9/2005 09:48:46 AM
MEDICAL OFFICER