

EXECUTIVE SUMMARY

NDA 20-010

LOTRISONE (betamethasone dipropionate and clotrimazole) LOTION

1. Introduction

Lotrisone (betamethasone dipropionate and clotrimazole) Lotion is a combination product containing an anti-fungal (clotrimazole) and a topical corticosteroid (betamethasone dipropionate) which is proposed by the Sponsor for use in the treatment of tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*. It is to be used twice daily and for four weeks for tinea pedis and for two weeks for tinea cruris and tinea corporis.

2. Regulatory History

NDA 18-827 was approved for Lotrisone Cream in 1984, based on clinical trials conducted comparing Lotrisone Cream, Lotrimin Cream, and Diprosone Cream in tinea pedis, tinea corporis, and tinea cruris. In these trials, Lotrisone Cream relieved signs and symptoms of tinea [erythema, maceration, scaling, pruritus, vesicles, papules, and pustules] more quickly than did Lotrimin Cream. The Lotrisone and Lotrimin Creams had different vehicle compositions.

The proposed development program for the Lotrisone Lotion formulation (with the same concentration of actives as Lotrisone Cream) was the following:

- A parallel-group comparison of active lotion and vehicle in tinea pedis.
- A parallel-group comparison of active lotion and vehicle in tinea cruris (safety and efficacy for treatment of tinea corporis to be interpolated from these two studies)
- A vasoconstrictor assay to compare Lotrisone Cream with Lotrisone Lotion and confirm availability of corticosteroid.

NDA 20-010 for Lotrisone Lotion was originally submitted to FDA on August 31, 1989. The Application was found Approvable on July 18, 1991 based on data submitted to the Lotrisone Cream NDA (18-827) and additional studies as provided for in the development plan and submitted to NDA 20-010. The Approvable Letter stated that the Sponsor was to provide further information and have satisfactory Manufacturing Establishment Inspection Reports prior to marketing. The only outstanding clinical issues identified in the Approvable Letter were updates to safety and labeling.

Due to difficulties in broader application of the vasoconstrictor assays with regard to both efficacy and safety, NDA 20-010 was the last NDA for which Agency allowed the use of such assays as a method to establish equivalence of steroid activity for products that contain a steroid in combination with another active ingredient.

The Sponsor submitted a response to the Approvable Letter on October 7, 1999.

3. Clinical Studies

3.1 Protocol Synopsis

Two multi-center, double-blind comparison studies of Lotrisone Lotion to its vehicle and one vasoconstrictor assay were submitted to this NDA.

Schering Study S-88-067 was a three-center study of patients with tinea pedis, conducted on patients age 12 and older, with BID application for 4 weeks. The patients were evaluated at baseline, 1, 2, 3, 4 and 6 weeks. The clinical status of the infection was examined, including signs and symptoms of erythema, maceration, scaling, pruritus,

vesicles, papules, and pustules. A global evaluation and mycology (KOH and cultures) were also done with screening and at each visit.

Schering Study S87-024 was a three-center study on patients with tinea cruris, conducted on patients age 12 and older, with BID application for 2 weeks. The patients were evaluated at baseline, 3 days, 1 week, 2 weeks, and 4 weeks. Scoring for signs and symptoms, global evaluation, and mycology was performed at these time points.

Schering studies C83-035-38/59/62 are three vasoconstriction studies involving 24 subjects each with 8 test sites per subject.

3.2 *Efficacy*

Lotrisone Lotion was superior to vehicle in anti-fungal and anti-inflammatory effects in the two clinical studies conducted. None of the subjects randomized to Lotrisone Lotion were infected with *Microsporum canis*.

The results from the vasoconstriction studies supported the conclusion that the vasoconstriction effect of betamethasone dipropionate 0.05%, in the proposed commercial Lotrisone Lotion formulation is comparable to that of Lotrisone Cream.

3.3 *Safety*

No serious adverse events were noted during the conduct of the two clinical trials submitted to this NDA. The Sponsor has agreed that Lotrisone Lotion will be labeled as a super-potent topical corticosteroid due to results from the vasoconstriction studies.

As no studies were performed on subjects under the age of 12, the Sponsor proposes the following Pediatric Use section for labeling (which is different from the current approved Lotrisone Cream labeling): "Lotrisone Lotion is not recommended for use in children under 12 years of age as the safety and effectiveness have not been established in well-controlled clinical studies in pediatric patients under 12 years. It is not to be used for diaper dermatitis. **NOT TO BE USED UNDER THE AGE OF 12 AND NOT TO BE USED IN DIAPER DERMATITIS...**"

4. *Safety of Lotrisone Cream (NDA 18-827)*

A report was compiled by FDA, Office of Postmarketing Drug Risk Assessment, regarding Adverse Events associated with use of Lotrisone Cream since its approval. The report concluded that Lotrisone is widely used in the United States and that adverse events are not rare. A large proportion of the adverse events reported were associated with off label use of the drug, in terms of age, indication for use, and length of use. Drug use data (IMS Health) indicate that about 20% of use of Lotrisone were seen in <12 year olds. Much of use in 0 to 1 year olds (> 7% of total use) was for diaper dermatitis despite labeling for Lotrisone Cream to the contrary: "Safety and effectiveness in children below the age of 12 have not been established with LOTRISONE Cream... The use of Lotrisone Cream in diaper dermatitis is not recommended."