Clinical Review of NDA 21-152 and 19-957 Supplements

NDA 21-152/ S-003 and S-004
NDA 19-957/ S/012

Submission dates:	6/19/14 and 7/18/2014 and 6/20/2014, 8/6/2014
SDN:	163 and 166 and 302, 303
RPM:	Phillips
Clinical:	Woitach/Kettl
Drug:	Cutivate (fluticasone propionate)
Pharmacologic Category:	Corticosteroid
Indication:	Atopic dermatitis/ (b) (4)
Dosage Form:	0.05% Lotion 0.05% Ointment
Route of Administration:	Topical
Sponsor:	Fougera Pharmaceuticals
Review date:	October 23, 2014
Review revised:	November 24, 2014
In DARRTS:	November 24, 2014

Regulatory Summary:
These related submissions contain the following:

- An amendment to the Changes Being Effected 30 Day (CBE-30) implementation supplemental application **(S-003)** for an additional increased package size, a 120 ml container of **Cutivate Lotion**.
- An amendment to the Prior Approval Supplement **(S-004)** to expand the indication of **Cutivate Lotion** to include treatment of patients 3 to 11 months of age. The efficacy supplement also proposes conversion of the label to comply with the physician labeling rule (PLR).
- A labeling supplement **(S-012)** which proposes conversion of the **Cutivate Ointment** label to comply with the physician labeling rule (PLR).

Background:
The Agency's August 2, 2012 Complete Response letter for S-003 stated that the deficiency precluding approval was that the applicant did not have an approved manufacturing site.

The Agency's July 18, 2012 Complete Response letter for S-004 stated that the deficiency precluding approval was that the applicant did not have an approved manufacturing site.

The applicant subsequently submitted supplement S-006 which provided for the manufacturing site transfer of Cutivate Lotion to Fougera's Hicksville, NY facility. Supplement S-006 was approved by FDA on April 24, 2013.

Review of outstanding manufacturing site issue:

Supplements S-003 and S-004 were reviewed by separate CMC reviewers.

- Dr. Hossein S. Khorshidi recommends approval of NDA 21-152/S-003 from a CMC perspective (9/30/14).
- Dr. Shulin Ding recommends approval of NDA 21-152/S-004 from a CMC perspective (9/30/14).

There were no outstanding clinical issues for NDA 21-152/S-003 and S-004. Approval of S-003 (clinical review 7/12/12) and S-004 (clinical review 10/26/10 and addendum 2/16/11) was contingent upon resolution of an acceptable manufacturing site. As of April 24, 2013, there is an approved manufacturing site to support approval of both supplements.

Also, the study submitted in NDA 21-152/S-004 to address PMC #1 in the 3/31/05 Cutivate Lotion approval letter adequately fulfills the post-marketing commitment requirement to conduct a deferred pediatric study under PREA in subjects aged 3 months to 1 year of age.

Reviewer comment: This reviewer also recommends approval for NDA 21-152/S-003 and S-004 pending agreed upon labeling. Labeling for Cutivate Lotion is described below.

Review of proposed labeling changes:

For PLR conversion of both Cutivate Lotion and Cutivate Ointment, it was determined that the Division's new "class label" template would apply. The applicant's proposed labeling was revised with the input of the review team. The approach taken was to recommend labeling consistent between the Cutivate products where applicable and to be consistent with the Division's steroid class labeling where appropriate. Labeling is currently in negotiations with the applicant. The finalized labeling which will be attached to the action letter will serve as a record of labeling agreed to by the clinical review team. See attached proposed labeling (appendix) which incorporates clinical recommendations. Pertinent changes in the Prescribing Information (PI) which require additional comment are discussed below.

Cutivate Lotion

Labeling of Cutivate Lotion was reviewed as part NDA 021152/S-003 and at that time DMEPA found the proposed container label and carton labeling acceptable.

1 INDICATIONS AND USAGE

With the recommended approval of S-004, the indications and usage should change from being indicted in patients 1 year of age or older to the following:

> CUTIVATE® Lotion is a corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age or older.

5 WARNINGS AND PRECAUTIONS

5.1 Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression and Other Adverse Endocrine Effects

Class warnings will be modified as per the steroid template.

5.3 Concomitant Skin Infections

(b) (4)

If skin infections are present or develop, an appropriate antimicrobial agent should be used. If a favorable response does not occur promptly, discontinue use of CUTIVATE® Lotion until the infection has been adequately controlled.

Reviewer comment: The steroid template recommends against including warnings on concomitant infections, as the team that developed the template thought this interferes with the practice of medicine. It is this reviewer's opinion to keep in this warning for the following reasons:

- *There may be an increased risk in the patient population due to age (>=3months)and disease state (atopic skin susceptible to bacterial colonized)*
- *It is the currently approved Cutivate label*
- *it is currently incorporated in other steroid labeling*

Information for Patients:
The following text has been deleted because it has been determined that the non-clinical data no longer supports this clinical risk.

(b) (4)

Cutivate Ointment
The above modifications to section 5 also apply to this product.

6.2 Postmarketing Experience

It was noted that postmarketing AEs related to the ointment formulation were included in the lotion labeling. However, there is not similar language in the ointment labeling. The applicant has been requested to provide information on postmarketing experience for this section of labeling.

Recommended Regulatory Action:
From a clinical standpoint, these applications (NDA 21-152/ S-003 and S-004; NDA 19-597/ S/012) are recommended for APPROVAL based on the conclusions of the CMC review that the Complete Response deficiencies have been adequately addressed, and once agreement on labeling is reached with the sponsor.

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/s/

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11/24/2014

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