CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-320

SUMMARY REVIEW

DIVISION DIRECTOR DECISIONAL REVIEW

Date	01Dec08
From	Susan J. Walker, M.D.
Subject	Division Director Decisional Review
NDA/BLA # Supp #	22-230/00
Proprietary / Established (USAN) names	EPIDUO™/ (adapalene and benzoyl peroxide)
Dosage forms / strength	Gel (0.1%/2.5%)
Proposed Indication	1. Treatment of acne vulgaris
Action:	*Approval*

1. Introduction

This application proposes the use of a topical combination gel containing adapalene 0.1% and benzoyl peroxide 2.5% for the treatment of acne vulgaris. There are no significant or controversial regulatory or scientific issues raised by this application. The ingredients adapalene and benzoyl peroxide have been previously approved for the treatment of acne vulgaris.

2. Background

The application proposes a product that combines two currently marketed active ingredients into a new gel formulation. The sponsor currently markets adapalene 0.1% gel, and has in this application combined 0.1% adapalene with benzoyl peroxide 2.5% in a gel vehicle. The combination must demonstrate the contribution of each component by comparison to the active ingredients and vehicle.

3. CMC

I concur that the propriety name and established name of the product as recommended by the CMC reviewer should be expressed as TRADENAME, established name, dosage form, and strength. There are no unresolved CMC issues. Facilities have acceptable site recommendations.

4. Nonclinical Pharmacology/Toxicology

There are no unresolved pharmacology/toxicology issues for this application.

5. Clinical Pharmacology/Biopharmaceutics

There are no unresolved clinical pharmacology issues for this application.

6. Clinical Microbiology

No studies were conducted.

7. Clinical/Statistical

7.1. General

Meaningful assessment of clinical improvement for the treatment of acne vulgaris in this application includes both an evaluation of the overall appearance of the patient, measured as an Investigator Global assessment (IGA) and an evaluation of acne vulgaris lesions, measured as inflammatory and non-inflammatory lesion counts. Safety assessments are provided by evaluation of local signs and symptoms and by evaluation of systemic absorption. Success for the investigators global assessment included at least a two grade improvement from baseline for the IGA score AND a week 12 evaluation of "clear" or "almost clear". Success for lesions counts included demonstration of improvement measured as absolute change and percent change from baseline.

The sponsor and Agency agreed upon a statistical analysis plan for study 18087 but did not agree on a plan prior to initiation of study 18084. For assessment of efficacy, the agreements reached on study 18087 were applied to study 18084. Both studies included four arms (the combination product, adapalene 0.1% in gel vehicle, benzoyl peroxide 2.5% in gel vehicle, and vehicle) and enrolled subjects with 20-50 inflammatory lesions and 30-100 non-inflammatory lesions at baseline.

7.2 Efficacy

The applicant has demonstrated by evaluation of an investigators global assessment and lesions counts that the combination product is superior to each monad and to placebo after 12 weeks of once daily treatment.

Investigator's Global Assessment (ITT_LOCF)

	EPIDUO Gel	*Adapalene 0.1% in vehicle gel*	*BZPO 2.5% in Vehicle gel*	*Vehicle Gel*
Study 18084 Success (%)	32 (21.5)	18 (12.2)	18 (12.1)	4 (5.6)
(p)		0.0291	0.0088	0.0023
Study 18087 Success (%)	125 (30.1)	83 (19.8)	92 (22.2)	47 (11.3)
(p)		0.001	0.0062	0.001

Lesion Counts (ITT_LOCF)

	EPIDUO™ Gel	*Adapalene 0.1% in vehicle gel*	*BZPO 2.5% in Vehicle gel*	*Vehicle Gel*
Inflammatory Lesion Counts				
N (Study 18094)	149	148	149	71
Mean Change	-16.0	-11.4	-10.5	-9.5
Mean % Change	-52.4	-39.9	-35.8	-31.8
p		<.001	<.001	<.001
N (Study 18087)				
Mean Change	-15.4	-12.3	-13.7	-8.7
Mean % Change	-53.4	-41.7	-47.6	-30.2
p		0.001	0.068	0.001
Non-inflammatory Lesion Counts				
N (Study 18094)	149	148	149	71
Mean Change	-23.4	-15.2	-13.7	-13.7
Mean % Change	-45.9	-29.6	-32.2	-27.8
p		<0.001	<0.001	<0.001
N (Study 18087)				
Mean Change	-24.6	-21.0	-19.2	-11.3
Mean % Change	-48.1	-40.8	-37.2	-23.2
p		0.048	<0.001	<0.001
Total Lesions				
N (Study 18094)	149	148	149	71
Mean Change	-39.3	-26.5	-24.1	-22.6
Mean % Change	-48.5	-34.0	-33.3	-29.7
p		<0.001	<0.001	<0.001
N (Study 18087)				
Mean Change	-39.9	-33.3	-33.0	-20.0
Mean % Change	-50.0	-41.3	-41.2	-26.1
p		0.0003	0.0004	<0.001

Based upon studies provided, including evaluation of the investigators global assessment and lesions counts, the sponsor has adequately demonstrated superiority of their combination product to the monads, adapalene 0.1% in vehicle gel and benzoyl peroxide 2.5% in vehicle gel, and to placebo gel. The totality of information provided by the applicant supports the approval of this product.

8. Safety

The safety database was adequate and there were no unexpected adverse events. Collection of adverse events and assessment of local tolerance did not reveal any unexpected safety signals.

9. Advisory Committee Meeting
The application was not presented to an advisory committee.

10. Pediatrics

Clinical studies were conducted in subjects 12 years of age and older. The applicant requested a waiver for subjects below age 9 and a deferral for subjects ages 9 to 11. The waiver and deferral requests were presented to PERC who concurred with the proposed plan. Deferred pediatric studies are required post marketing studies under section 505B (a). The applicant is required to conduct a multi-center randomized placebo controlled double blind study to evaluate the safety and efficacy of EPIDUO™ Gel administered once daily for the treatment of subjects ages 9-11 years with acne vulgaris. Final report submission is due July 1, 2011.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Final product labeling has been accepted by the sponsor, including package insert, tube and container.

13. Conclusions and Recommendations

I concur with the recommendations of the primary reviewers and team leaders. NDA 22-320, EPIDUO gel will be approved for the treatment of acne vulgaris with the agreed upon labeling.

There are no outstanding unresolved issues, and my decision is consistent with the recommendations from the review team. There are no recommendations for additional post marketing risk management activities.

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/s/

Susan Walker
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DIRECTOR