CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-470

CHEMISTRY REVIEW(S)

NDA 21-470

Finacea (azelaic acid) Gel, 15%

Berlex Laboratories, Inc.

Mamta Gautam-Basak, Ph.D.
Division of Dermatologic and Dental Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-470

2. REVIEW #1

3. REVIEW DATE: December 19, 2002

4. Mamta Gautam-Basak, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-470/000	2002-03-20
NDA 21-470/BZ	2002-06-06
NDA 21-470/BC	2002-10-14
NDA 21-470/BC	2002-12-06

7. NAME & ADDRESS OF APPLICANT:

Name:	Berlex Laboratories, Inc.
Address:	340 Changebridge Road P. O. Box 1000 Montville, NJ 07045-1000
Representative:	John Hegarty
Telephone:	(973) 487-2016

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Finacea
b) Non-Proprietary Name (USAN): Azelaic Acid
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 15% (w/w)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X__Rx ___OTC

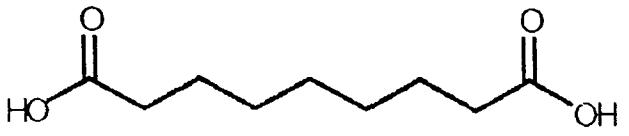
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nonanedioic acid; 1, 7-Heptanedicarboxylic acid
Molecular Formula: C9H16O4
Molecular Weight: 188.22 CAS No.: 123-99-9



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	Schering AG		1	Adequate	Chem. Rev. #4 on 12/6/02	The DMF was ADEQUATE (Chem. Rev #3) Updates reviewed in Rev.#4. No IR letter
	II			1	Adequate	Chem. Rev. #2 on 12/06/02	Adequate to support DMF
	IV			1	Adequate	Chem. Rev #1 on 8/2/2002	Adequate (minor IR letter)
	IV			1	Adequate	Chem. Rev #1, 8/2/2002	Adequate (minor IR letter)
	III			4			
	III			4			
	III			4			
	III			7			No review needed since are
	III			7			No review needed since are
	III			7			No review needed since are

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION No.	DESCRIPTION
IND	61,324	Azelaic Acid Gel, 15%
IND	[redacted]	
NDA	20-428 (approved 9/13/1995)	Azelex (azelaic acid) Cream, 20%

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	12-16-02	Mamta Gautam-Basak, Ph.D.
Pharm/Tox	Specification for non-compendial excipient [redacted] acceptable	10-20-02	Barbara Hill, Ph.D.
Biopharm	Comparative in-vitro release testing between the clinical and to-be-marketed batches not required (since the batch 03002 used in the important clinical studies was manufactured at the proposed commercial site)	10-17-02	Chandra S. Chaurasia, Ph.D.
LNC	N/A		
Methods Validation	Pending	12-19-02	Mamta Gautam-Basak, Ph.D.
OPDRA	Trademark not acceptable	12-18-02	Marcie Ann Lee, Pharm.D.
EA	CE acceptable	12-18-02	Mamta Gautam-Basak, Ph.D.
Microbiology	Approvable	10-18-2002	Bryan Riley, Ph.D.

The Chemistry Review for NDA 21-470

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From chemistry, manufacturing, and controls (CMC) stand point an approvable (AE) action is recommended, pending a satisfactory cGMP status of all the manufacturing and testing facilities.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, azelaic acid (AzA) is a naturally occurring saturated dicarboxylic acid. AzA is currently approved for use in the US in a topical cream formulation under Allergan's approved NDA 20-428. AzA is used in both the formulations. Detailed CMC information pertaining to purification and of the drug substance is provided by reference in the Type II drug master file There are no pending deficiencies for this DMF. The DMF continues to be ADEQUATE to support NDA 20-428 as well as the subject NDA. obtains azelaic acid from located in the USA. is synthesized from oleic acid that is derived from beef tallow. Since the material is obtained from a free country there is no risk as far as issues are concerned (see Chemistry Assessment).

There are no changes to the drug substance specification as approved under NDA 20-428.

The proposed drug product, Finacea contains micronized azelaic acid in a concentration of 15% in a gel base. The formulation is developed to contain a low amount of and a high amount of for of the drug itself. Although the vehicle is translucent the drug product is opaque. Polyacrylic acid or serves as the in the formulation. The formulation also contains a moisturizer (lecithin), an emollient (medium chain triglycerides), and polysorbate 80 as an . Benzoic acid is used as a preservative at a concentration of and propylene glycol serves as a EDTA serves as a ; that can cause gradual reduction in the of the gel. The production processes

and controls described for the commercial product are similar to those used for production of primary stability batches. The specification for the drug product is based on the recommendations in ICH Q6A document.

The primary container is described as [redacted] tubes with a [redacted] screw cap. The filled tubes are packaged as 30-g, 50-g and a 3-g physician sample. The packaging components used are the same as approved for Azelex Cream, 20% under NDA 20-428.

Stability data are provided for [redacted] production scale batches [redacted], manufactured at the facility that will be used for the to-be-marketed product and in the proposed market containers. The drug product will be marketed as 30-g and 50-g tubes. [redacted] month data are provided for [redacted] (30-g and 50-g) batches, at long term storage conditions (25°C/60%RH) as well as intermediate (30°C/70% RH) and [redacted] month data for the 3-g physician sample size. [redacted] month data at accelerated conditions (40°C/75%RH) are provided for all [redacted] batches packaged in all sizes (30-, 50-, and 3-g tubes). All results met the specification with no trend change in values observed (see Chemistry Assessment).

A twenty-four (24) month expiration dating period is supported based on [redacted] months of long term data provided for three production size primary batches using statistical analysis. Regression analysis results (at 95% confidence limits) on micropenetration value, and on azelaic acid and benzoic content supports a 24 month expiration date for the commercial product packaged as 30- and 50-g and the sample size packaged as 3-g tube.

The to-be-marketed formulation and the formulation, SH H 655BA used in the pivotal clinical and pharmacological clinical studies are exactly the same.

B. Description of How the Drug Product is Intended to be Used

FINACEA is indicated for topical application in the treatment of inflammatory papules and pustules [redacted] of rosacea. A thin layer of FINACEA is applied twice daily, in the morning and evening, to the entire affected areas and gently massaged into the skin. The duration of use of FINACEA can vary from person to person and depends on the severity of rosacea. In the majority of patients, improvement of the dermatosis was observable after 4 weeks.

C. Basis for Approvability or Not-Approval Recommendation

The proposed formulation is exactly the same that was used in *pivotal* clinical studies. The batches used in *pivotal* studies are manufactured at the same site (using same controls) as proposed for the to-be-marketed product. The specification for the drug product failed to include a control on related substances. Since no degradants were reported in the stability studies (even with the use of a validated GC method), the applicant will be asked to correct this omission in a supplemental application. All other deficiencies noted during review are

resolved. An overall recommendation regarding the GMP compliance of the manufacturing and testing facilities is pending.

III. Administrative

A. Reviewer's Signature

Chemist:
Mamta Gautam-Basak, Ph.D.

B. Endorsement Block

Chemistry Team Leader:
Wilson H. DeCamp, Ph.D.

C. CC Block

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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/

Mamta Gautam-Basak
12/19/02 03:09:39 PM
CHEMIST

Wilson H. DeCamp
12/19/02 03:15:58 PM
CHEMIST
concur with reviewer recommendation; action should be AE because OC final evaluation has not been received