CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-234

CHEMISTRY REVIEW(S)

NDA 21-234

Flector® Patch
(diclofenac epolamine topical patch)
1.3%

Institut Biochimique SA (IBSA)

Sue-Ching Lin

Review Chemist

Office of New Drug Quality Assessment
Pre-Marketing Division III, Branch V
for
Division of Anesthesia, Analgesia, and Rheumatology Products

Table of Contents

CMC Review Data Sheet

1. NDA 21-234

2. REVIEW #: 3

3. REVIEW DATE: 23-Jan-2007

4. REVIEWER: Sue-Ching Lin

5. PREVIOUS DOCUMENTS:

Chemistry Review #1 Cycle	Document Date
Original submission	18-Dec-2000
Five Amendments	From 06-Feb-2001 to 22-Jun-2001
Chemistry Review #1	11-July-2001
Chemistry Review #2	17-Oct-2001

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed in this Cycle	Document Date
Resubmission (AZ)	27-Jul-2006
Amendment (BZ) (package insert in Word format)	12-Sep-2006
Amendment (BZ) (response to FDA 8/31/06 IR)	14-Sep-2006
Amendment (BZ) (response to FDA 12/14/06 IR)	28-Dec-2006
Amendment (BZ) (response to FDA 1/8/07 & 1/18/07 IR)	23-Jan-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Institut Biochimique SA (IBSA)
Address:	Via Del Piano Casella Postale 266 CH-6915 Pambio-Noranco Switzerland
Representative:	Clarence E. Jones, Ph.D. 8602 Mossford Drive Huntington Beach, CA 92646
Telephone:	(714) 963-0078 (phone/fax)

CMC Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Flector® Patch (proposed in this resubmission)
b) Non-Proprietary Name: diclofenac epolamine topical patch
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 2 (new salt, classified as Type 2 per CDER hand book: http://www.fda.gov/cder/handbook)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), resubmission
No reference listed drugs. This submission was determined by the clinical division as 505(b)(2), based upon literature only.

10. PHARMACOL. CATEGORY: NSAID

11. DOSAGE FORM: patch

12. STRENGTH/POTENCY: 1.3%

13. ROUTE OF ADMINISTRATION: topical

14. Rx/OTC DISPENSED: √ Rx ___OTC

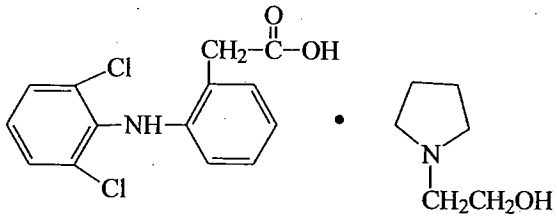
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

√ Not a SPOTS product

CMC Review Data Sheet

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

2-[(2,6-dichlorophenyl)amino]benzeneacetic acid, 2-(pyrrolidin-1yl)ethanol salt



$C_{20}H_{24}Cl_2N_2O_3$ MW 411.3

Diclofenac epolamine

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	REVIEWER
	II		diclofenac epolamine	1	Adequate	1/23/07	Sue-Ching Lin
	II			1	Adequate	1/10/07	Sue-Ching Lin
	II			3	Adequate	9/1/06	Bing Wu
	IV			1	Adequate	1/22/07	Sue-Ching Lin

[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)

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	49,459	Diclofenac Epolamine
NDA	20-612	Lidoderm

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Biometrics	N/A		
EES	Acceptable	8/29/06	S. Adams
Pharm/Tox	Acceptable for Perfume Dalin PH	1/9/07	Dan Mellon
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	The proprietary name "Flector®" is acceptable	1/12/07	Tselaine Jones-Smith
EA	Categorical exclusion (see review #1)		Sue-Ching Lin
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 21-234

The Executive Summary

I RECOMMENDATIONS

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls perspective, this NDA is recommended for approval.

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

None

II SUMMARY OF CMC ASSESSMENTS

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

(1) Drug Substance

The active ingredient, diclofenac epolamine, is a new salt of diclofenac. The name "epolamine" is the established name recognized in the USP Dictionary for 1-pyrrolidineethanol, which forms salt with diclofenac acid. Detailed information regarding the drug substance is referenced to DMF The DMF holder has responded to the FDA deficiencies that were identified in the previous review cycle. DMF have been reviewed by this reviewer and found to be adequate to support this NDA.

Diclofenac epolamine is water soluble. A 10% solution gives a pH of

(2) Drug Product

The drug product is a topical patch. It consists of an adhesive material containing 1.3% of diclofenac epolamine, which is sandwiched between a non-woven polyester backing and a polypropylene film. The polypropylene film is a release liner that is to be removed prior to topical application of the patch to the skin.

Each adhesive patch, in the size of 10 cm x 14 cm, contains 180 mg of diclofenac epolamine. The patch is packaged in resealable envelopes with zip-lock seal, each containing 5 patches.

In addition to the active ingredient, the adhesive mass also contains 17 excipients with defined functions such as [redacted] Each patch also contains [redacted] of perfume Dalin PH.

The adhesive [redacted] is prepared [redacted]

The proposed manufacturer, Teikoku Sieyaku Co., Japan, also manufactures Lidoderm topical patch (NDA 20-612), which was approved in March 1999.

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

Flector® Patch will be dispensed by prescription only. It is proposed to be indicated for the relief of pain due to strains, sprains, and contusions [redacted] The patch is to be applied to intact skin one patch at a time within a 12-hour period. [redacted]

Updated stability data were submitted in this review cycle, which include stability results for three batches of drug product stored at 25°C/60%RH (39 months) and 40°C/75%RH (9 months). These batches were in commercial production size manufactured at the proposed commercial manufacturing facility. The submitted stability data support the proposed expiration period of 36 months.

C. Basis for Approvability or Not-Approval Recommendation

The CMC information of the drug substance was referenced to DMF — The DMF holder has adequately addressed the deficiencies that were identified in the previous review cycle.

All the inactive ingredients are USP/NF materials with the exception of 1,3-butylene glycol, sodium polyacrylate, and perfume Dalin PH. Both 1,3-butylene glycol and sodium polyacrylate have been used in approved drug products as indicated in the FDA database for approved inactive ingredients. Information regarding perfume Dalin PH is referenced to DMF — which has been reviewed by this reviewer and found to be adequate to support the use of this perfume in the patch, as all of the ingredients in this perfume are listed in the CFR as GRAS as flavoring agents in food or essential oils/extracts that are found in foods.

The drug product manufacturing process and specification have been reviewed and found to be adequate. Updated labeling was submitted in this review cycle. Labeling deficiencies that were identified by this reviewer have been addressed by the applicant in the amendments.

The Division of Medication Errors and Technical Support (DMETS) has no objections to the use of the proposed proprietary name "Flector®."

The manufacturing, testing and packaging facilities remain unchanged from the last review cycle. A re-evaluation of all the facilities for the drug substance and drug product was submitted by this reviewer to the Office of Compliance. An overall acceptable recommendation was issued by the Office of Compliance on 8/29/06.

III ADMINISTRATIVE

A. Reviewer's Signature: electronically signed in DFS

Sue-Ching Lin, M.S., R.Ph.

B. Endorsement Block: electronically signed in DFS

Ravi Harapanhalli, Ph.D.

C. CC Block: entered electronically in DFS

29 Page(s) Withheld

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/s/

Sue Ching Lin
1/25/2007 07:10:00 PM
CHEMIST

Ravi Harapanhalli
1/25/2007 07:13:13 PM
CHEMIST

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
HFD-550
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-234 **DATE REVIEWED:** 17-Oct-2001

REVIEW # 2 **REVIEWER:** Sue-Ching Lin

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	18-Dec-2000	19-Dec-2000	03-Jan-2001

NAME & ADDRESS OF APPLICANT:
Institut Biochimique SA (IBSA)
745-D Camden Avenue
Campbell, CA 95008-4146

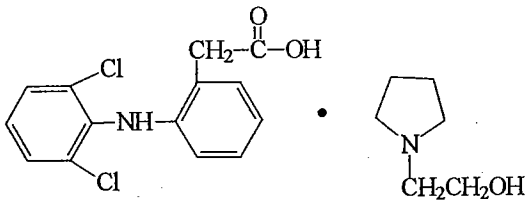
DRUG PRODUCT NAME

Proprietary:	none
Established:	diclofenac epolamine patch
Code Name/#:	DHEP
Chem.Type/Ther.Class:	2S

PHARMACOL. CATEGORY: NSAID
DOSAGE FORM: patch
STRENGTHS: 1.3% w/w
ROUTE OF ADMINISTRATION: topical
DISPENSED: _X_ Rx ____OTC
SPECIAL PRODCUTS ____Yes _X_ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

2-[(2,6-dichlorophenyl)amino]phenylacetic acid, 1-(2-hydroxyethyl)pyrrolidine salt



$C_{20}H_{24}Cl_2N_2O_3$ MW 411.3

Diclofenac epolamine

REMARKS:
On October 15, 2001, the Office of Compliance issued an "acceptable" recommendation for the inspection of facilities involved in the manufacturing and control of the drug substance and drug product. Please see attached establishment evaluation report.

CONCLUSIONS & RECOMMENDATIONS:

The CMC portion of this NDA is still inadequate and thus NOT approvable. Please refer to chemistry review #1 for the deficiencies.

cc:
Orig. NDA# 21-234
HFD-550/Division File
HFD-550/JSmith/Sue Lin
HFD-550/Gould
HFD-550/MO/JStaufer
HFD-550/Pharm/HAmouzadeh
HFD-550/PK/Bashaw
HFD-550/SChoi
DNDC3_IO

Sue-Ching Lin, M.S., R.Ph.
Chemist, HFD-550/830

John Smith, Ph.D.
Chemistry Team Leader, HFD-550

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/s/

Sue Ching Lin
10/17/01 10:50:58 AM
CHEMIST

John Smith
10/17/01 11:17:24 AM
CHEMIST

First Cycle 10/17/01

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
HFD-550
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-234 **DATE REVIEWED:** 05-Jul-2001

REVIEW # 1 **REVIEWER:** Sue-Ching Lin

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	18-Dec-2000	19-Dec-2000	03-Jan-2001
Amendments	05-Feb-2001 (BC)	06-Feb-2001	11-Feb-2001
	16-Mar-2001 (BC)	19-Mar-2001	20-Mar-2001
	12-Apr-2001 (BZ)	13-Apr-2001	18-Apr-2001
	17-May-2001 (BC)	21-May-2001	24-May-2001
	22-Jun-2001 (BC)	26-Jun-2001	27-Jun-2001

NAME & ADDRESS OF APPLICANT:
Institut Biochimique SA (IBSA)
745-D Camden Avenue
Campbell, CA 95008-4146

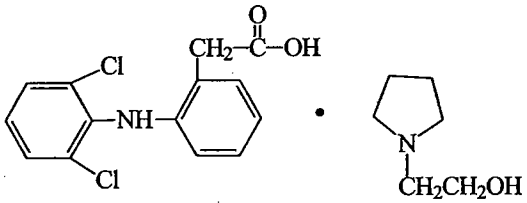
DRUG PRODUCT NAME

Proprietary:	none
Established:	diclofenac epolamine patch
Code Name/#:	DHEP
Chem.Type/Ther.Class:	2S

PHARMACOL. CATEGORY: NSAID
DOSAGE FORM: patch
STRENGTHS: 1.3% w/w
ROUTE OF ADMINISTRATION: topical
DISPENSED: _X_ Rx ____OTC
SPECIAL PRODCUTS ____Yes _X_ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

2-[(2,6-dichlorophenyl)amino]phenylacetic acid, 1-(2-hydroxyethyl)pyrrolidine salt



$C_{20}H_{24}Cl_2N_2O_3$ MW 411.3

Diclofenac epolamine

SUPPORTING DOCUMENTS:

IND# 49,459
DMF# — for diclofenac epolamine

RELATED DOCUMENTS: NDA 20-612, Lidoderm

REMARKS:

1. The drug substance is a new salt of diclofenac. The name "epolamine" is an established name recognized in the USP Dictionary (page 1104 of the 2000 edition) for 1-pyrrolidineethanol, which forms salt with diclofenac.

2. No proprietary name was proposed for this drug product. The name "DHEP Patch" was used as an abbreviation in the NDA application.

3. Drug substance: Detailed information on the drug substance is referenced to DMF — for diclofenac epolamine. A summary of the DMF information was provided in the drug substance section of the NDA. DMF — has been reviewed by this reviewer and found to be deficient. The DMF holder has been notified of the deficiencies.

4. Drug product: The finished dosage form is a topical patch. It is comprised of an adhesive material, containing the active ingredient, which is uniformly applied to one side of a non-woven polyester felt backing and covered with a polypropylene film as a release-liner. The release-liner is removed prior to application of the patch to the skin. There are numerous deficiencies with the drug product section of this NDA. Please refer to the end of this review for a list of deficiencies.

5. Establishment evaluation was requested for each site used for manufacturing and control of the drug substance and drug product, as listed in section A-2 and B-3 of this review. No response has been received from Office of Compliance yet.

6. Container/closure systems: The container closure system is an airtight envelope, formed by

7. Environmental assessment: A categorical exclusion has been submitted in the 2/5/01 amendment.

8. Methods validation is pending. Methods validation packages have not been sent to the FDA laboratories, due to deficiencies in specifications of drug substance and drug product.

9. Labeling: The labeling is deficient. Please refer to the end of review notes for deficiencies.

CONCLUSIONS & RECOMMENDATIONS:

The applicant has not provided adequate information on the chemistry, manufacturing, and control of the drug product. Numerous deficiencies were noted in the review of the CMC portion of the application. They are listed at the end of this review. Establishment evaluation request was sent on 1/9/01 and the inspection is still pending. Methods validation packages have not been sent to the FDA laboratories, due to deficiencies in specifications of drug substance and drug product. From the CMC standpoint, this NDA is NOT approvable.

cc:
Orig. NDA# 21-234
HFD-550/Division File
HFD-550/JSmith/Sue Lin
HFD-550/Gould
HFD-550/MO/JStaufer
HFD-550/Pharm/HAmouzadeh
HFD-550/PK/Bashaw
HFD-550/SChoi
DNDC3_IO

Sue-Ching Lin, M.S., R.Ph.
Chemist, HFD-550/830

John Smith, Ph.D.
Chemistry Team Leader, HFD-550

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/s/

Sue Ching Lin
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CHEMIST

John Smith
7/11/01 03:27:22 PM
CHEMIST