CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-862

CHEMISTRY REVIEW(S)

NDA 21-862

NEVANAC™ (nepafenac ophthalmic suspension) 0.1%

ALCON RESEARCH, INC.

Libaniel Rodriguez, Ph.D.
Division of Anti-infective and Ophthalmology Products

HFD-520

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-862

2. REVIEW #: 1

3. REVIEW DATE: 11-Aug-2005

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 49,924	05-Feb-1996

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-Feb-2005
BC	20-Jun-2005
BC	27-Jul-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Alcon Research, Inc.

Address: 6201 South Freeway
Fort Worth, TX 76134-2099

Representative: Angela C. Kothe

Telephone: 817 551 4933

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Nepafenac Ophthalmic Suspension, 0.1%
b) Non-Proprietary Name (USAN): Nepafenac
c) Code Name/# (ONDC only): AI-6515
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Anti-inflammatory and analgesic

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 0.1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X__Rx ___OTC

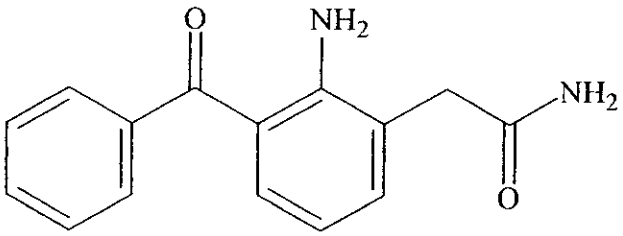
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Chemical Name(s): 2-Amino-3-benzoylbenzeneacetamide
2-(2-Amino-3-benzoylphenyl)acetamide

Structure:



Molecular Formula: $C_{15}H_{14}N_2O_2$
Molecular Mass: 254.28

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II		Drug Substance	1	Inadequate Adequate	30-Jun-2005 01-Aug-2005	Comments sent to holder Response Adequate
—	III			4	N/A		
—	III			4	N/A		

[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: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	26-Apr-2005	Office of Compliance
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Acceptable Adequate Validation by applicant. No need to send MV package to District Lab.	01-Jul-2005	Libaniel Rodriguez
OPDRA			
EA	Acceptable Categorical exclusion	01-Jul-2005	Libaniel Rodriguez
Microbiology	Approval	09-Jun-2005	V. Pawar

The Chemistry Review for NDA 21-862

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the viewpoint of CMC, 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 Chemistry Assessments

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

The drug product Nevanac is a sterile ophthalmic suspension with a 0.1% concentration of the nonsteroidal anti-inflammatory drug substance nepafenac. The product is indicated for the — treatment of pain and inflammation associated with cataract surgery and is intended for used three times daily, beginning one day prior to cataract surgery, continued on the day of surgery and for two weeks after surgery. The drug product is packaged in Alcon's oval DROP-TAINER® package system consisting of a 4 mL bottle and — plug made of natural low density polyethylene (LDPE), a — closure made of gray (for topical ophthalmic medications) polypropylene (PP) and a label made of paper with — — adhesive. Tamper evidence is provided by a — shrink band. —

—

The drug product is formulated with nepafenac as the active ingredient, benzalkonium chloride, carbomer 974P, tyloxapol, edetate disodium and sodium chloride as excipients, sodium hydroxide and hydrochloric acid for pH adjustment and purified water as the vehicle. The manufacturing process for the drug product involves — — for a final sterile drug product. Pre-clinical and clinical formulations differed only in the process by which the drug substance was manufactured. The drug substance for the pre-clinical formulations contained small amounts of impurities which were substantially eliminated of minimized by — in the drug substance manufacturing process for the

clinical formulations. No comparability protocols were implemented since the only difference in formulations was the improvement of the impurity profile for the drug substance.

The drug substance Nepafenac, 2-Amino-3-benzoylbenzeneacetamide, Molecular Formula: $C_{15}H_{14}N_2O_2$, Molecular Mass 254.28, is a yellow crystalline or powder material . The melting point is and observed for this material.

The drug substance Nepafenac (amfenac amide), pro-drug to amfenac sodium (marketed drug product in Japan), is a new molecular entity. The details for the synthesis, characterization, physical and chemical properties impurity profile and stability of this drug substance were referenced in this application to type II drug master file (DMF) number Appropriate letter of authorization to reference DMF dated November 23, 2004 is included in this application.

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

The commercial (trade) size for Nevanac is a 3 mL fill in a 4 mL bottle. The The product is recommended of use as one drop in the affected eye three times a day for approximately 16 days beginning the day prior to surgery for an approximate total of 48 applications. At an average size of 40 µL per drop (~ 2000 µl total use), the trade size (3 mL) for this drug product provides ample supply for the duration of treatment.

Aside from shaking the drug product bottle for redispersion of the suspension prior to application, no unusual preparations are needed for the use of this drug product.

Based on the stability data provided in this application, the retest period recommended for the drug substance is when stored at , the shelf life recommended for the 3 mL fill drug product is eighteen months when stored between 2°C and 25°C and ambient humidity.

C. *Basis for Approvability or Not-Approval Recommendation*

Issues concerning acceptance criteria and testing for the drug substance were satisfactorily resolved during this review cycle. Issues concerning acceptance criteria for drug product were resolved satisfactorily as well.

III. Administrative

A. Reviewer's Signature

Libaniel Rodriguez, Review Chemist/ 11-Aug-2005

B. Endorsement Block

Libaniel Rodriguez, Review Chemist/ 11-Aug-2005
Linda Ng, Chemistry Team Leader/11-Aug-2005
Raphael Rodriguez, Project Manager/11-Aug-2005

B. CC Block

See DFS distribution list.

46 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Libaniel Rodriguez
8/11/05 10:22:17 AM
CHEMIST
Review #1 AP

Linda Ng
8/11/05 10:28:54 AM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21862/000
Org Code : 520
Priority : 1P

Sponsor: ALCON
6201 SOUTH FREEWAY
FORT WORTH, TX 761342099

Stamp Date : 28-FEB-2005
PDUFA Date : 31-AUG-2005
Action Goal :
District Goal: 01-NOV-2005

Brand Name : NEVANAC(NEPAFENAC OPHTHALMIC SUSPENSION)
Estab. Name:
Generic Name: NEPAFENAC SUSPENSION 0.1%
Dosage Form: (SUSPENSION)
Strength : 0.1%

FDA Contacts:			
	R. RODRIGUEZ	Project Manager (HFD-550)	301-827-2519
	L. RODRIGUEZ	Review Chemist (HFD-830)	301-827-2069
	L. NG	Team Leader (HFD-830)	301-827-2511

Overall Recommendation: ACCEPTABLE on 26-APR-2005by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : CFN : 1610287 FEI : 1610287
ALCON LABORATORIES INC
6201 SOUTH FREEWAY
FORT WORTH, TX 76115

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SNI OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-APR-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities: [ ]

Profile :	CSN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	04-FEB-05		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		
