CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-938**

CHEMISTRY REVIEW(S)

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
HFD-550

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-938

DATE REVIEWED: 12-Aug-1999

REVIEW # 1

REVIEWER: Sue-Ching Lin

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	15-Dec-1998	16-Dec-1998	21-Dec-1998
Amendments	17-Feb-1999	Reformatted package insert	
	28-Jul-1999	Response to FDA's comments on drug substance and drug product specifications, and additional stability data (24 months)	
	06-Aug-1999	Response to FDA comments on dissolution and drug substance specifications	
	09-Aug-1999	Revised methods validation packages	

NAME & ADDRESS OF APPLICANT:

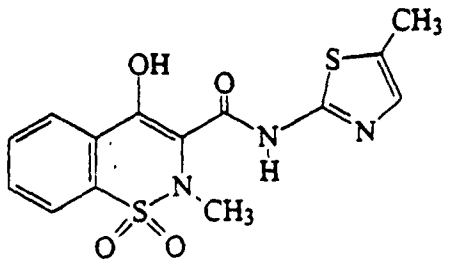
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

DRUG PRODUCT NAME

Proprietary:	Mobic®
Established:	meloxicam tablets
Code Name:	UH AC 62XX
Chem.Type/Ther.Class:	1S
PHARMACOL. CATEGORY:	NSAID
DOSAGE FORM:	tablet
STRENGTHS:	7.5 mg
ROUTE OF ADMINISTRATION:	oral
DISPENSED:	X Rx ___ OTC
SPECIAL PRODUCTS:	___Yes X No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide



CAS 71125-38-7

$C_{14}H_{13}N_3O_4S_2$ M.W. 351.4

SUPPORTING DOCUMENTS:

DMFs: See table below -

DMF#	Type	Holder	Item/Component	Review Date	Status	LOA
	II			8/4/99*	Adequate	12/3/98
	III			7/30/99*	Adequate	4/21/97
	III			4/2/99	Adequate	8/11/98
	III			2/24/99	Adequate	2/19/98
	III			6/30/99	Adequate	3/13/98
	III			8/6/99*	Adequate	7/21/98
	III			**		1/27/98
	III			5/11/99	Adequate	2/24/98
	III			6/16/98	Adequate	2/24/98
	III			9/3/98	Adequate	3/4/98
	III			10/13/98	Adequate	2/19/98
	III			7/22/99*	Adequate	2/18/98

* DMFs reviewed by this reviewer for this NDA.
** Outer shell resin is not in contact with the drug product and has no impact on drug product stability. See stability report ("assessment of packaging material" is one of the stability parameters).

REMARKS:

1. Meloxicam is a new molecular entity in the U.S.. The proprietary name "Mobic" has been found to be acceptable by the CDER Labeling and Nomenclature Committee on April 9, 1999.

2. Drug substance: Detailed information on the drug substance is referenced to [redacted] for meloxicam. A summary of the DMF information was provided in the drug substance section of the NDA. [redacted] has been reviewed by this reviewer. Deficiencies in manufacture and stability of the drug substance were conveyed to the DMF holder on June 23, 1999. The 7/29/99 and 8/2/99 DMF amendments responded **adequately** to the deficiencies. See DMF review for details.

3. Drug product: The finished dosage form is a 7.5 mg tablet. Description of composition, quality control of all the ingredients, manufacturing procedure for the drug product, quality control for the finished dosage form, justification for the tests and specifications, and container/closure systems are provided. Dissolution specification [redacted] was established from the results of dissolution development studies and supported by the stability data. It was found to be acceptable after the 7/19/99 and 7/30/99 discussions between this reviewer and the biopharm reviewer Dr. Veneeta Tandon and the biopharm

team leader Dr. Dennis Bashaw. Twenty-four months stability data were submitted to support expiration period of 30 months for drug product packages. The stability protocol is not acceptable. The applicant has agreed, during the 8/4/99 telephone conference, to revise the stability protocol and submit it in an amendment.

4. Establishment evaluation was requested for each site used for manufacturing and control of the drug substance and drug product The overall EES recommendation for this NDA is acceptable.

5. Container/closure systems:
Multi-dose bottles of 30 tablets and 100 tablets
Unit-dose packages of 100 tablets per carton (10 blister cards of 10 tablets each)
The sample pack will contain two tablets per blister card inside an individual carton.

6. Environmental assessment: A categorical exclusion has been submitted under 21 CFR § 25.31(b).

7. Methods validation is pending. Methods validation packages were revised in response to the reviewer's comments and in accordance with the FDA guideline. The revised packages were submitted on 8/9/99. Copies of methods validation packages were sent to Philadelphia District Laboratory and St. Louis Laboratory on 8/11/99 for validation of the methods by the FDA laboratories.

8. Labeling: See review notes for comments, which were conveyed to the applicant on 8/11/99.

CONCLUSIONS & RECOMMENDATIONS:

The applicant has not provided adequate information on the chemistry, manufacture and control of the drug product. Several deficiencies were noted in the review of the CMC portion of the application. They are listed at the end of this review. The deficiencies have been communicated to the applicant. The applicant has not provided their response to the deficiencies yet. Methods validation has not been completed by the FDA laboratories but is not required for approval of the NDA. From the CMC standpoint, this NDA is approvable pending satisfactory response to the deficiencies.

/S/ 8/12/99

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

/S/ 8/13/99

Hasmukh Patel, Ph.D.
Chemistry Team Leader, HFD-550

cc:
Orig. NDA 20-938
HFD-550/Division File
HFD-550/HPatel /Sue Lin
HFD-550 CLewin
HFD-550 KJohnson/JHyde
HFD-550 JYang/Lu
HFD-550 VTandon/DBashaw
HFD-830 CChen

NDA 20-938, Mobic Tablets

Addendum to Chemistry Review # 1

Section B-8, Stability Protocol and Commitment of Drug Product Deficient

a) Testing Material for Each Analysis:
30 tablets: 4 bottles
100 tablets: 1 bottle
Blisters: 10 blister cards (10 tablets each)

b) Storage Conditions and Test Time Points:

First year of manufacture: 3 batches of each packaging material, stored at 25°C/[redacted] tested at 0, 6, 12, 24, 36, 48, and 60 months

All batches produced in the upcoming 4 production years: stored at 25°C/[redacted] and analyzed at the beginning, middle, and end of the expected shelf life

All batches stored in the sixth year: analyzed at the interval of 0, 6, 12, 24, 36, 48, and 60 months

c) Stability Commitment:

1) Perform follow up stability studies
2) Withdraw from the market any lots found to fall outside the approved specifications.
3) Stability report will be issued upon request

Evaluation:

1. All of the testing frequencies described above are not acceptable. Stability testing frequency for commercial batches should be every 3 months over the first year, every 6 months over the second year, and then annually.

2. During the telephone conference between this reviewer and the applicant on 7/28/99, Dr. Pat Watson, Technical Director of Drug Regulatory Affairs of Boehringer Ingelheim, stated that she was not sure whether the term "all batches" meant all batches that are produced or all batches that are placed on stability. The protocol did not indicate the number of batches that will be placed on stability each year.

3. Stability reports should be submitted in the annual report. The stability commitment is inadequate to state that stability reports will be issued upon request.

At the 8/4/99 telephone conference with the applicant (Mr. Alan McEmber and Dr. Patricia Watson), the company indicated that the stability protocol and commitment submitted in volume 3, pages 135-142, will be revised and provided in an amendment to be submitted later.

During the 8/6/99 telephone conference between the company and this division (Dr. Hasmukh Patel, Chemistry Team Leader, and this reviewer), it was agreed that the company will continue the stability study on the three primary stability batches (those are in commercial production batch size), and place at least one production batch per year on stability after approval. In other words, the company does not need to place three more production batches on stability for the changes in [redacted] bottle supplier and bottle resin.

/S/ 8/17/99

Sue-Ching Lin
Review Chemist, HFD-550/830

/S/ 8/18/99

Hasmukh Patel, Ph.D.
Chemistry Team Leader, HFD-550

cc:
Orig. NDA 20-938
HFD-550/Divison File
HFD-550/HPatel/Sue Lin
HFD-550/CLewin
HFD-830/CChen

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

NDA #: 20-938

DATE REVIEWED: 08-Dec-1999

REVIEW # 2

REVIEWER: Sue-Ching Lin

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL[1]	15-Dec-1998	16-Dec-1998	21-Dec-1998
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	06-Aug-1999	Response to FDA comments on dissolution and drug substance specifications	
	09-Aug-1999	Revised methods validation packages	
Amendments[2]	09-Sep-1999	Revised stability protocol	
	21-Sep-1999	Electronic copy of draft package insert	
	19-Oct-1999	Draft package labeling	
	23-Nov-1999	Commitments for professional sample blister package	
	07-Dec-1999	Revised Stability Protocol	

[1] submissions covered in chemistry review #1
[2] submissions covered in this review

NAME & ADDRESS OF APPLICANT:
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
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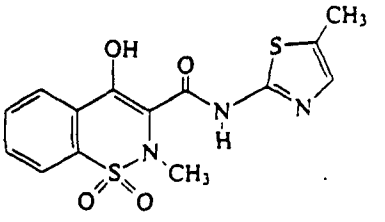

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* DMFs reviewed by this reviewer for this NDA.

**Outer shell resin is not in contact with the drug product and has no impact on drug product stability. See stability report ("assessment of packaging material" is one of the stability parameters).

REMARKS:

These amendments responded to the chemistry deficiencies listed in chemistry review #1. The applicant has adequately addressed the deficiencies.

CONCLUSIONS & RECOMMENDATIONS:

The CMC section of this NDA is acceptable. This NDA may be approved. Methods validation has not been completed by the FDA laboratories but is not required for approval of the NDA. The letter to the applicant should include the standard methods validation paragraph.

cc:
Orig. NDA 20-938
HFD-550/Division File
HFD-550/Mitra/Sue Lin
HFD-550/TZeccola
HFD-550/KJohnson/JHyde
HFD-550/JYang/Lu
HFD-550/VTandon/DBashaw
HFD-830/CChen

/S/ 12/8/99

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

/S/ 12/8/99

Amit Mitra, Ph.D.
Acting Chemistry Team Leader, HFD-550