Boehringer Ingelheim

specification. The batches 701528A and 701530A were tested according to stage 2 requirements after 18 months and the results meet the new specification (mean values above 75%, minimum individual value 73.1%). Although only six tablets were tested from batch 701529A after 18 months, it is likely that this batch would also have met the stage 2 specification with additional testing.

After 24 months at 30°C [redacted] the blister-packaged tablets fail the new specification (mean values between 71.8 % and 72.9 %).

Please note that 24 months storage at the intermediate condition of 30°C [redacted] greatly exceeds the ICH stability guideline (Q1A) requirements, *i.e.*, ICH requires only 12 months of data at the intermediate storage condition. Based on the longer-term data, it can be reasonably concluded that the tablets will meet the new dissolution specification requirements following 12 months storage at 30°C [redacted]

After 24 months storage at 25°C [redacted] the data fail the new specification from time to time for stage 1 testing, but the mean values all exceed 80 %. Thus, for stage 2 the new specification would be fulfilled.

Based on these data, we propose a revised expiration dating period of 24 months for tablets packaged in [redacted] blisters.

Attached is an electronic copy of the text (excluding the testing specification documents and the stability report) of this amendment. The electronic copy is provided in Word 97 format.

A copy of this amendment has been submitted to the Stoneham, Massachusetts inspectional district office for Boehringer Ingelheim Pharmaceuticals, Inc., as required in 21 CFR 314.60(c).

If there are any questions, please contact me at the phone number shown above. Thank you.

Sincerely,

Alan V. McEmber
DRA Senior Associate Director

Attachments: FDA Facsimile dated July 19, 1999 from Constance Lewin, M.D.
Diskette with electronic files

Desk Copy: Dr. Sue-Ching Lin (2 copies)

DUPLICATE
BP

Boehringer Ingelheim

Karen Midthun, MD., Acting Director
Division of Anti-Inflammatory, Analagesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd
Rockville, MD 20850

ORIG AMENDMENT

Boehringer Ingelheim
Pharmaceuticals, Inc.

July 28, 1999

RE: MOBIC® Tablets
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION :
Population PK Analysis

Dear Dr. Midthun,

Reference is made to a Biopharm Review request sent via facsimile dated July 15, 1999 from Dr. Constance Lewin (copy attached), in which Dr. Veneeta Tandon requested information regarding the population PK analysis. Further reference is made to our facsimile dated July 23, 1999 responding to the request from Dr. Tandon.

We are now following up with an official copy being submitted as an amendment to the NDA.

If you have any further questions, please contact me.

Sincerely,

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Alan McEmber, M.S.
Telephone 203-798-4366
Telefax 203-791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

July 30,1999

Re: Mobic® Tablets
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Electronic Copy of Draft Labeling (Package Insert)

Alan McEmber, M.S.
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun,

Reference is made to a telephone contact dated 7/29/99 between Dr. Constance Lewin of your Division and myself in which we agreed to provide an electronic copy of the draft package insert in Word 97.

Please find attached a paper copy and an electronic copy of the annotated and unannotated package insert. The package insert is the same as the version submitted in the original NDA, except for the addition of the AEs identified in the four-month safety update and editorial/format changes.

If you have any further questions, please contact me.

Sincerely,

Fay Pack for
Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Constance Lewin (3)

G:\DRA\Meloxicam\ElecDraftLabel.doc

ORIGINAL

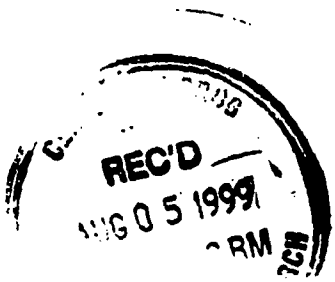
ORIG AMENDMENT

BP

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850



August 03,1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
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900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9388

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

Dear Dr. Midthun:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed is a paper copy of the revised toxicology reports listed below. Also enclosed is a diskette containing the text portion (not including the appendices/graphs) of each of the revised reports.

U89-0219 Oral and Intravenous Acute Toxicity Studies with Meloxicam (UH-AC 62) in Rats.(Previously submitted in Amendment to NDA 20-938 on 2/4/99; Vol. 2.009, P. 315).

U88-0048 Determination of the ALD_{50} of UH-AC62 XX in the Rat Following Intravenous Administration.(Previously submitted in Amendment to NDA 20-938 on 2/4/99; Vol. 2.009, p. 339).

U89-0635 Approximative Acute Toxicity (ALD_{50}) With UH-AC62 XX In Minipigs After Oral Administration. (Previously submitted In Amendment to NDA 20-938 on 2/4/99; Vol. 2.009, P. 359).

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Boehringer Ingelheim

U91-0618 Approximative Acute Toxicity (ALD_{50}) of UH-AC 62 XX By Intravenous Administration in Micropigs. (Previously Submitted in Amendment to NDA 20-938 on 2/4/99; Vol. 2.010, p. 104).

If you have any further questions, please contact me.

Sincerely.

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

ORIGINAL
BP

Boehringer Ingelheim

ORIG AMENDMENT

Boehringer Ingelheim
Pharmaceuticals, Inc.

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

August 06,1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

Response to FDA Request for Information:
Revised Toxicology Report

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6252
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun,

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed is a paper copy of the revised toxicology report listed below. Also included is a diskette containing the text portion (not including the graphs/tables) of the revised report.

U82-0509 Teratogenicity Study with the Substance UH-AC 62 XX in Rabbits Segment II. (Previously submitted in Amendment to NDA 20-938 on February 4, 1999, Vol. 2.047, P. 1).

If you have any further questions, please contact me.

Sincerely,

David R. Budd for AVM

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

G:\DRA\Meloxicam\cvrletU820509toxrpt.doc

ORIGINAL

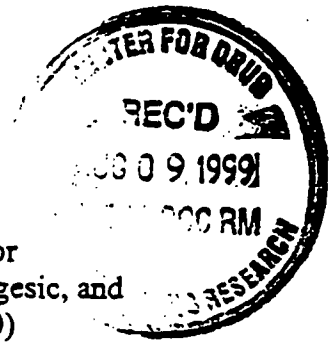
BC

CMC AMENDMENT

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals Inc.

Food and Drug Administration
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Document Control Room N115
9201 Corporate Boulevard
Rockville, MD 20850



August 06, 1999

Attention: Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)

MOBIC® (meloxicam) 7.5 mg Tablets
NDA 20-938
CMC Amendment / Response to FDA Request for Information

Patricia Watson
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E-Mail pwatson@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Sir or Madam:

Please amend CMC Amendment dated July 28, 1999, with the following chemistry, manufacturing and controls (CMC) information:

Section 4.1.9 Drug Substance Controls
Section 4.1.9.2 Specifications and Test Methods
(CMC Amendment dated July 28, 1999, page 4 - 5)

Reference is given to an August 3, 1999, telephone discussion with Dr. Sue-Ching Lin, Review Chemist, in which Dr. Lin requested that the regulatory specifications for the drug substance identify the USP/NF compendial methods for the compendial test parameters, e.g., pH and Sulfated Ash. She noted that alternative methods may be employed by the company, but advised that the USP/NF methods are the official methods. In the event of a dispute as to whether or not the drug substance meets the regulatory specifications, the USP/NF methods are the referee methods.

According to Dr. Lin's request, enclosed in this amendment is a revised Section 4.1.9.2, where TABLE 4.1.9.2:1 is amended to designate the USP/NF methods for the compendial tests.

Boehringer Ingelheim

Section 4.2.6 **Drug Product Controls**
Section 4.2.6.2 **Specifications and Test Methods**
(CMC Amendment dated July 28, 1999, pages 34, 36 - 71)

Please refer to FDA's August 2, 1999, facsimile (copy attached), from the Biopharmaceutics and Chemistry Reviewers, in which they recommend a dissolution specification of [redacted] based on their review of the dissolution data presented in the CMC Amendment dated July 28, 1999.

We agree to change the dissolution specification from [redacted] Enclosed in this amendment is a revised TABLE 4.2.6.2:1, which presents the regulatory specifications amended with the revised dissolution specification.

BIPKG's Testing Specification Number [redacted] is enclosed with this amendment. This document has been amended to revise the handwritten notation concerning the dissolution specification, and now shows the dissolution specification as [redacted]

Attached is an electronic copy of the text (excluding the Testing Specification document) of this amendment. The electronic copy is provided in Word 97 format.

A copy of this amendment has been submitted to the Stoneham, Massachusetts inspectional district office for Boehringer Ingelheim Pharmaceuticals, Inc., as required in 21 CFR 314.60(c).

If there are any questions, please contact me at the phone number shown above. Thank you.

Sincerely,

Patricia Watson

Patricia Watson
DRA Technical Director

Attachments: FDA Facsimile dated August 2, 1999
Diskette with electronic files

Desk copy: Dr. Sue-Ching Lin (2 copies)

Certification of Submission of Field Office Copy

Boehringer Ingelheim Pharmaceuticals, Inc. hereby certifies that a copy of this Chemistry amendment has been sent to the FDA District Office in Stoneham, Massachusetts, in accordance with 21 CFR 314.60(c).

Patricia Watson

Patricia Watson
DRA Technical Director
Drug Regulatory Affairs

August 6, 1999

Date

ORIGINAL

Boehringer Ingelheim

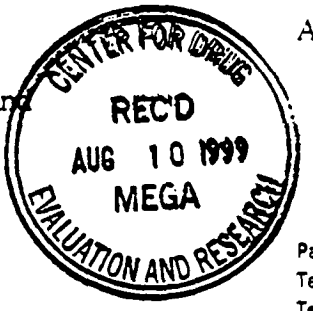
BC

Boehringer Ingelheim
Pharmaceuticals Inc.

Food and Drug Administration
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Document Control Room N115
9201 Corporate Boulevard
Rockville, MD 20850

ORIG AMENDMENT

August 09, 1999



Attention: Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)

Patricia Watson
Telephone 203-791-6233
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MOBIC® (meloxicam) 7.5 mg Tablets
NDA 20-938
CMC Amendment / Response to FDA Request for Information / Recompilation of Methods Validation Package

Dear Sir or Madam:

As requested by Dr. Sue-Ching Lin, Review Chemist, we have recompiled the Methods Validation Package of our NDA. Please amend Section 4.5. METHODS VALIDATION PACKAGE of our NDA with the enclosed information.

In accordance with the *FDA Guideline for Submitting Samples and Analytical Data for Methods Validation* (2/87), the methods validation package consists of information reproduced from our [redacted] as amended, our NDA original application, and NDA CMC amendments.

An introductory section in this amendment, titled "Organization of the Methods Validation Package", identifies the original location (DMF/NDA/Amendment, Volume, page) of the pages reproduced in this amendment.

Two copies of this amendment (Archival and Chemistry Review) are submitted.

A copy of this amendment has also been submitted to the Stoneham, Massachusetts inspectional district office for Boehringer Ingelheim Pharmaceuticals, Inc., as required in 21 CFR 314.60(c).

If there are any questions, please contact me at the phone number shown above. Thank you.

Boehringer Ingelheim

Sincerely,

Patricia Watson

Patricia Watson
DRA Technical Director

Attachments – Form 356(h)
Certification of Submission of Field Office Copy

Enclosure – 1 volume

Desk copy: Dr. Sue-Ching Lin (2 copies)

Certification of Submission of Field Office Copy

Boehringer Ingelheim Pharmaceuticals, Inc. hereby certifies that a copy of this Chemistry amendment has been sent to the FDA District Office in Stoneham, Massachusetts, in accordance with 21 CFR 314.60(c).

Patricia Watson

Patricia Watson
DRA Technical Director
Drug Regulatory Affairs

Aug. 9, 1999

Date

ORIGINAL

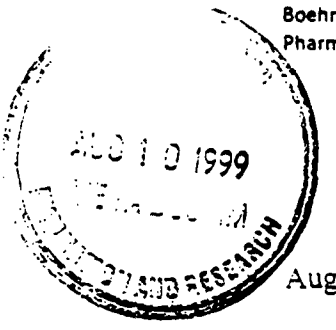
B2

Boehringer Ingelheim

ORIG AMENDMENT

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.



August 9, 1999

Alan McEmber
Senior Associate Director
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Telefax (203) 791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

Other: Analysis of Risk of Clinically Serious Upper Gastrointestinal Complications among Patients Receiving Meloxicam

Dear Dr. Midthun:

Reference is made to the telephone conference call of July 12, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc.(BIPI) . In the teleconference a conditional 3-month extension of the NDA review was granted based upon BIPI submitting major revisions of the toxicology reports to the Division by September 16. 1999. Also in the teleconference, BIPI discussed its intention to submit a clinical report to the NDA which provides an analysis of the risk of clinically serious upper gastrointestinal complications associated with meloxicam treatment. This assessment was conducted by a blinded. independent clinical committee from a review of the clinical trial database. Dr. John Hyde agreed that the Division would accept this clinical amendment for review. Enclosed is the report entitled, "Risk of Clinically Serious Upper Gastrointestinal Complications among Patients Receiving Meloxicam," (Report No. U99-31230).

Based upon the findings of the report, BIPI is submitting a proposed revision of the 'Warnings' and 'Clinical Trials' sections of labeling for review and consideration by the Division. We appreciate the efforts in your review of the NDA and this amendment. If you have any further questions, please contact me at the number above.

Sincerely,

for Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Kent Johnson
\\BIP_US_MEDICAL\VOL2\GROUPDIR\DRA\Meloxicam\NDA Communications\9let0809 PUB Letter with labeling proposal.doc

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

August 5,1999

AMENDMENT
BP

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
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E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

Dear Dr. Midthun:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed is a paper copy of the revised toxicology reports listed in the Table of Contents. Also enclosed is a CD-Rom containing a non-clinical report on pharmacokinetics in the rat (U87-0431).

If you have any further questions, please contact me.

Sincerely,

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

ORIGINAL

Desk Copy: Dr. Josie Yang

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ORIGINAL

BP

Boehringer Ingelheim

ORIG AMENDMENT

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

August 09,1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

Response to FDA Request for Information:
Revised Toxicology Report

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun,

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed is a paper copy of the revised toxicology report listed below. Also included is a diskette containing the text portion (not including the graphs/tables) of the revised report.

U92-0692 **Reproduction Study With Meloxicam (UH-AC 62 XX) In Rats Dosed Orally During the Period of Organogenesis Segment II [Previously submitted in Amendment to NDA 20-938 on February 4, 1999, Vol. 2.045, P. 288].**

If you have any further questions, please contact me.

Sincerely,

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

ORIGINAL

BB

Boehringer Ingelheim

NDA ORIG AMENDMENT

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

August 11, 1999

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Location of Assay Validation Reports for Drugs Other Than Meloxicam

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun:

Reference is made to the Division's fax dated August 09, 1999 in which a request was made to provide the specific location of the assay validation reports for drugs other than meloxicam from the clinical drug interaction studies section. Additional reference is made to the February 04, 1999 submission (Amendment #1) in which Boehringer resubmitted the study reports for NDA Section 6 (Human Pharmacokinetics and Bioavailability).

Section 6.7.2.6 (Human Pharmacokinetics and Bioavailability - Effect of Comedication) from the February 04, 1999 NDA submission has been reviewed to determine the location of the assay validation reports for drugs other than meloxicam.. A table summarizing the location of these reports, and the NOMEM report (U97-2656), is provided in Attachment 1 of this submission. Please note that in some instances only meloxicam was measured and therefore there is no comedication assay validation report.

The assay validation report for warfarin (from study 107.141; U95-2256) which was specifically mentioned in your fax, was inadvertantly omitted from the NDA submission. The report has been requested from our offices in Germany and will be available next week for submission.

Boehringer Ingelheim

As requested by Dr. Lewin of your Division, this submission has also sent been sent via fax to facilitate distribution of the information to the Reviewer.

If you have any further questions, please contact me.

Sincerely,

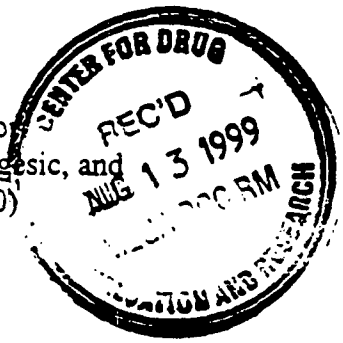
for

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

ORIGINAL

BP

Boehringer Ingelheim



Boehringer Ingelheim
Pharmaceuticals, Inc.

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

August 12, 1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

NDA ORIG A... ...MENT

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed is a paper copy of the revised toxicology reports listed below. Also enclosed is a diskette containing the text portion (not including the graphs/tables) of the revised reports.

U92-0308 Reproduction Study with Meloxicam (UH-AC 62 XX) in Rats Dosed Orally During Perinatal and Postnatal Period of Organogenisis. Segment III [Previously Submitted in Amendment to NDA 20-938 on February 4, 1999, Vol. 2.048, Pg. 169]. The Division's corresponding volume number is 3.048.

U92-0428 UH-AC 62 XX: Immunogenicity Study after Subcutaneous Plantar Administration in [redacted] Mice [redacted] [Previously Submitted in Amendment to NDA 20-938 on February 4, 1999, Vol. 2.038, Pg. 178]. The Division's corresponding volume number is 3.038.

Boehringer Ingelheim

If you have any further questions, please contact me.

Sincerely,

J Malony for

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

ORIGINAL

BP

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

NDA ORIGINAL AMENDMENT

August 13, 1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

Alan McEmber
Senior Associate Director
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E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed is a paper copy of the revised toxicology reports listed below. Also enclosed is a diskette containing the text portion (not including the graphs, tables) of the revised reports.

U90-0358 Intracutaneous sensitization with the Substance UH-AC 62 XX in the Guinea Pig. [Previously Submitted in Amendment to NDA 20-938 on February 4, 1999, Vol. 2.038, Pg. 62]. The Division's corresponding volume number is 3.038.

U91-0903 Reproduction Study with UH-AC 62 XX in Rats Dosed Orally Before Mating and During Early Period of Gestation. Segment I [Previously Submitted in Amendment to NDA 20-938 on February 4, 1999, Vol. 2.044, Pg. 190]. The Division's corresponding volume number is 3.044.

Boehringer Ingelheim

If you have any further questions, please contact me.

Sincerely,

Theresa Maloney for

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

ORIGINAL

BB

Boehringer Ingelheim

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

August 13, 1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

NDA ORIG AMENDMENT

RESPONSE TO FDA REQUEST FOR INFORMATION:
Warfarin Assay Validation Report (16/95-05.WN)

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun:

Reference is made to the Division's fax dated August 09, 1999 in which a request was made to provide the specific location of the assay validation reports for drugs other than meloxicam from the clinical drug interaction studies section. Additional references are made to Boehringer's response to that fax on August 11, 1999 and a telephone call between Dr. Lewin of your Division and Ms. Maloney of Boehringer on August 12, 1999.

As agreed with Dr. Lewin on August 12th, Boehringer is submitting the warfarin assay validation report (16/95-05.WN) which was inadvertently omitted from clinical study 107.141 (U95-2256).

The formal internal process at Boehringer requires an amendment to include study 16/95-05.WN as Appendix 15.9.3.1.2 of the main report, U95-2256. However, in order to expedite our response to your request, an advance copy of the warfarin assay validation report (16/95-05.WN) is being submitted. Completion of the formal amendment and internal archiving process will not change the data of study 16/95-05.WN.

Details of the warfarin assay validation report are below:

Report No.	16/95-05.WN
Title:	Quantitative determination of (R), (S)-Warfarin in Human Plasma by [redacted]
Date of Report:	June 14, 1995

Boehringer Ingelheim

If you have any further questions, please contact me.

Sincerely,

Therese Maloney for

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Desk copy to: Dr. Dan Wang
FDA
CDER/OCPB/DPEIII
HFD 880
Room N363
9201 Corporate Blvd.
Rockville, MD 20850

DUPLICATE

ORIG AMENDMENT

BP

Boehringer Ingelheim

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

August 17, 1999

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed is a paper copy of the revised toxicology report listed below. Also enclosed is a diskette containing the text portion (not including the tables) of the revised report.

U92-0610 UH-AC 62 XX: Comparative in vitro Determination of the Phototoxic Activity of Different Non-Steroidal Anti-Inflammatory Compounds. (Previously Submitted in Amendment to NDA 20-938 on 2/4/99, Vol. 2.038, Pg. 204).

If you have any further questions, please contact me.

Sincerely,

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

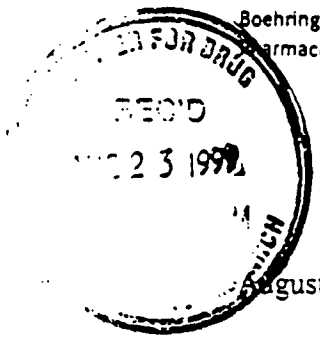
G:\DRA\Meloxicam\NDA Communications\9let0817 revised tox reports.doc

ORIGINAL

Boehringer Ingelheim

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and ORIG AMENDMENT
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

BP



Boehringer Ingelheim
Pharmaceuticals, Inc.

August 19, 1999

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

Dear Dr. Midthun:

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed is a paper copy of the revised toxicology report listed below. Also enclosed is a diskette containing the text portion (not including the end of text graph tables) of the revised report.

USS-0001 Lutzen L, Eckenfels A, Bauer M, Puschner H. Chronic Toxicology Study on the Substance UH-AC 62 XX in Rats by Oral Administration Over a Period of 18 Months. (Previously Submitted in Amendment to NDA 20-938 on 2/4/99, Vol. 2.015, Pg. 1).

If you have any further questions, please contact me.

Sincerely,

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

G. DRA\Meloxicam\NDA Communications\9let0819 revised tox reports.doc

Boehringer Ingelheim

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

BM

Boehringer Ingelheim
Pharmaceuticals, Inc.

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938

August 20, 1999

RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Midthun:

Reference is made to the NDA Amendment dated August 9, 1999, in which Boehringer Ingelheim Pharmaceuticals, Inc., (BIPI) provided an analysis of risk of clinically serious upper gastrointestinal complications among patients receiving meloxicam. Further reference is made to the telephone discussion of August 17, 1999 between Dr. Kent Johnson, of your division, Dr. Paul Gagnier, Mr. Jim Love and myself of BIPI in which we discussed your request to perform additional statistical analysis of the risk of serious upper gastrointestinal events restricted to osteoarthritis controlled trials that contained meloxicam at doses of 7.5 mg or 15 mg. BIPI provided this additional analysis in a facsimile to Dr. Kent Johnson on August 18, 1999. This information is now being officially submitted to the NDA as an amendment.

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262

E-Mail amcember@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

If you have any further questions, please contact me.

Sincerely,

Alan V. McEmber
Sr. Associate Director
Drug Regulatory Affairs

ORIGINAL

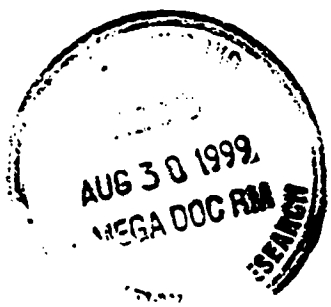
Boehringer Ingelheim

ORIG AMENDMENT

BP

Boehringer Ingelheim
Pharmaceuticals, Inc.

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850



August 27, 1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
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900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed is a paper copy of two revised toxicology reports listed below. A diskette containing the text portion (not including the end of text graph/tables) of these revised reports is also enclosed.

U87-0199 Chronic Toxicity Study on the Substance UH-AC 62 XX With Oral Administration to Mini-Pigs for 52 Weeks. (Previously Submitted in Amendment to NDA 20-938 on 2/4/99, Vol. 2.025. Pg. 1).

U88-0093 Chronic Toxicity Study on UH-AC 62 XX in Comparison with Piroxicam in Rats After Oral Administration Over a Period of 12 Months. (Previously Submitted in Amendment to NDA 29-938 on 2/4/99, Vol. 2.019. Pg. 1).

Boehringer Ingelheim

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

Additionally, we are submitting revised summaries of the reports listed below. The original reports are included with the revised summaries for ease of review. The diskette contains the electronic portion of the summaries.

U90-0509 Investigation of the Acute Toxicity of Stressed UH-AC 62 XX Solution (Decomposition 4.65%) by Intravenous Administration to Rats. (Previously submitted In Amendment to NDA 20-938 on 2/4/99, Vol 4/99, Vol. 2.010, Pg. 29.

U94-2131 UH-AC 62 XX (Meloxicam): Single Dose Toxicity Study (ALD_{50}) of BIBO 8032 NA, a Metabolite of UH-AC 62 XX in Rats After Intravenous Administration. (Previously submitted In Amendment to NDA 20-938 on 2/4/99, Vol. 2.010, Pg. 122).

U96-0299 Single Dose Toxicity Study of UH-AC 110 SE, AF-UH 1 XX And DS-AC 2 NA (Metabolites of UH-AC 62 XX) in Rats by Intravenous Administration. (Previously submitted In Amendment to NDA 20-938 on 2/4/99, Vol. 2.010, Pg. 57).

If you have any further questions, please contact me.

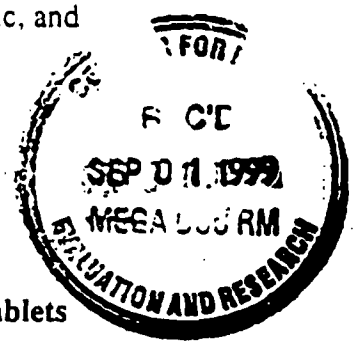
Sincerely,

Alan V. McEmber
Senior Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

Boehringer Ingelheim

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850



Boehringer Ingelheim
Pharmaceuticals, Inc.

ORIG AMENDMENT
BP

August 30,1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Summaries

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail
Amcember@rdg.boehringeringelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed are revised Executive Summaries of the seven reports listed below. The original reports are included with the revised summaries for ease of review. A diskette containing the electronic portion of each of the Executive Summaries is also enclosed.

US0-0054 Mutagenicity Study With The Substance UH-AC 62 XX in the Ames Test. (Previously Submitted in Amendment to NDA 20-938 on 2/4/99. Volume 2.049, Pg. 13).

US8-0540 Mutagenicity Study With UH-AC 62 XX in the S. Typhimurium and E. Coli/Mammalian Microsome Assay (Ames Test). (Previously submitted in Amendment to NDA 20-938 on 2/4/99 Volume 2.049. Pg. 31).

US4-0633 Mutagenicity Study With The Substance UH-AC 62 XX in the V79 (HGPRT) Test. (Previously submitted in Amendment to NDA 20-938 on 2/4/99, Volume 2.049, Pg. 56).

ORIGINAL

Boehringer Ingelheim

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Summaries

US9-0094 Mutagenicity Study With UH-AC 62 XX: Chromosomal Aberrations in Human Lymphocytes *in vitro*. (Previously submitted in Amendment to NDA 20-938 on 2/4/99, Volume 2.049, Pg. 89).

US3-0069 Mutagenicity Study With The Substance UH-AC 62 XX in the Micronucleus Test in Mice. (Previously submitted in Amendment to NDA 20-938 on 2/4/99, Volume 2.049, Pg. 118).

U92-0301 UH-AC 62 XX: Mutagenicity Study in the Mouse Bone Marrow [redacted] Assay After Oral Treatment. (Previously submitted in Amendment to NDA 20-938 on 2/4/99, Volume 2.049, Pg. 136).

US4-0220 Mutagenicity Study With The Substance UH-AC 62 XX in the [redacted] in Mice. (Previously submitted in Amendment to NDA 20-938 on 2/4/99, Volume 2.049, Pg. 160).

If you have any further questions, please contact me.

Sincerely,

Alan V. McEmber
Senior Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

G:\DRA\Meloxicam\NDA Communications\letrevisedtoxsum.doc

ORIGINAL

ORIG AMENDMENT

Boehringer Ingelheim

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

September 3, 1999

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

Dear Dr. Midthun:

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail amcember@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports.

Enclosed is a paper copy of two revised toxicology reports listed below. A diskette containing the text portion (not including the end of text graph/tables) of these revised reports is also enclosed.

US1-0061	Subacute Toxicity Study on the Substance UH-AC 62 XX With Oral Administration to Rats for 3 Months (Previously Submitted in Amendment to NDA 20-938 on 2/4/99, Vol. 2.011, Pg. 1).
US3-0068	Study of the Substance UH-AC 62 XX for Embryotoxicity in Rabbits Segment II - Supplementary Study. (Previously Submitted in Amendment to NDA 29-938 on 2/4/99, Vol. 2.048, Pg. 1).

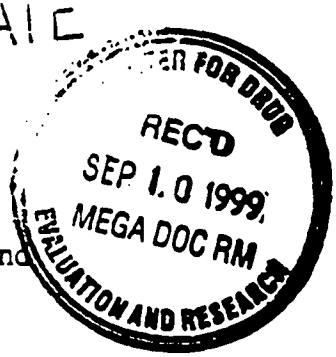
If you have any further questions, please contact me.

Sincerely,

Alan V. McEmber
Senior Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

DUPLICATE



Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals Inc.

Food and Drug Administration
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Document Control Room N115
9201 Corporate Boulevard
Rockville, MD 20850

September 09, 1999

Attention: Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)

Patricia Watson
Telephone 203-791-6233
Telefax 203-791-6262
E-Mail pwatson@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

MOBIC® (meloxicam) 7.5 mg Tablets
NDA 20-938
CMC Amendment / Response to FDA Request for Information

Dear Sir or Madam:

Reference is given to a July 27, 1999, telephone discussion with Dr. Sue-Ching Lin, Review Chemist, in which Dr. Lin requested that we amend our NDA with a revised stability protocol and stability commitment for post-approval stability studies.

According to Dr. Lin's request, a revised stability protocol and stability commitment was sent to Dr. Lin via facsimile on September 1, 1999, for her preliminary review and comment. Enclosed in this amendment is a revised **Section 4.2.9.4 Post-Approval Stability Protocol and Stability Commitment**, which incorporates a change requested by Dr. Lin based on her preliminary review. This revised stability protocol and stability commitment replaces the information submitted in Section 4.2.9.4 of our original NDA.

Attached is an electronic copy of this amendment. The electronic copy is provided in Word 97 format.

A copy of this amendment has been submitted to the Stoneham, Massachusetts inspectional district office for Boehringer Ingelheim Pharmaceuticals, Inc., as required in 21 CFR 314.60(c).

If there are any questions, please contact me at the phone number shown above. Thank you.

Boehringer Ingelheim

Sincerely,

Patricia Watson

Patricia Watson
DRA Technical Director

Attachments – Form 356(h)
Certification of Submission of Field Office Copy
Diskette with electronic file

Enclosure

Desk copy: Dr. Sue-Ching Lin (1 copy)

ORIGINAL

ORIG AMENDMENT

Boehringer Ingelheim

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

September 10, 1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

Response to FDA Request for Information:
Revised Toxicology Report

Alan McEmber
Senior Associate Director
Telephone (203) 798-5366
Telefax (203) 791-6252
E-Mail
amcember@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun,

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) in which specific concerns by the pharmacology reviewer, Dr. Josie Yang, were discussed. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which BIPI agreed to provide revised NDA toxicology reports to address Dr. Yang's concerns.

A total of 10 reports are now included in this update. Of these, BIPI has included a duplicate copy of one report (U93-0609) in which the legibility is improved. The remaining 9 reports[1] each include an executive summary which was written to aid in their review. BIPI has attached copies to the summary of the original reports referenced in the executive summary. A diskette containing the electronic portion of each of the revised Executive Summaries is included.

The location of the reports is found in a table of contents attached to this cover letter.

---

[1] Executive summaries are included of the following reports:

U88-0002	U89-0184	U92-0310
U88-0427	U82-0080	U92-0788
U90-0408	U85-0018	U80-0053

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

Boehringer Ingelheim

Response to FDA Request for Information:
Revised Toxicology Report

Please note that unlike earlier rewritten reports that have been submitted after the May 14th meeting, some of the tables in the reports forwarded in this submission contain bilingual text. The Corporate toxicologists reviewed the reports containing the bilinqual text to ensure their legibility and navigability are not compromised.

If you have any further questions, please contact me.

Sincerely,

Alan V. McEmber
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

Boehringer Ingelheim

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

ORIG AMENDMENT
BZ

October 19, 1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Draft Package Labeling

Alan McEmber
Senior Associate Director

Telephone (203) 798-4366
Telefax (203) 791-6262

E-Mail:
amcember@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun:

Reference is made to the following communications between your Division and Boehringer Ingelheim Pharmaceuticals, Inc (BIPI):

- Facsimile dated August 11, 1999 from Dr. Constance Lewin of your Division that provided the chemistry review labeling comments on the draft package labeling provided in the application. (Attachment A)

- Facsimile dated September 13, 1999 from BIPI that made changes to the draft package labeling based upon the FDA's August 11th comments. (Attachment B)

- Telephone discussion dated October 4, 1999 between Dr. Sue-Ching Lin, FDA Review Chemist, and Alan McEmber (BIPI) on the draft package labeling submitted in the September 13, 1999 facsimile.

- Telephone contact dated October 6, 1999 between Dr. Sue-Ching Lin, Alan McEmber (BIPI) and Patricia Watson (BIPI) concerning the package labeling and wording. Also discussed was the supporting documentation required for a 2 tablet professional sample blister card.

As agreed in the October 6, 1999 telephone call, we are now providing draft copies of the package labeling. The labeling is the same as what was submitted in the September 13, 1999 facsimile unless otherwise noted.

ORIGINAL

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938
October 19, 1999

Boehringer Ingelheim

Attached are the following labeling:

1. Bottle Labels:

   - **30 count trade** (4103520)
   - **100 count trade** (4103510)
   - **30 count professional sample** (4103500)

     The label differs from the 9/13/99 version. Added is the logo for Abbott Laboratories along with the marketed by statement of "Abbott Laboratories, North Chicago, IL 60064." The graphics color bar width is reduced.

2. Blister Pack Labels:

   - **Trade blister pack of 100 tablets: 10 tablet blister foil card** (5627150) **and outer carton** (5717466).

     The label differs from the 9/13/99 version. The font size for the statement "100 unit dose tablets" is reduced on the front and back panel of the outer carton.

   - **Professional Sample blister pack of 2 tablets: blister card** (5627150) **and outer carton** (5717465).

     The label differs from the 9/13/99 version. Added on both the blister card and on the outer carton is the statement, "Blisters are not child-resistant." Added to the outer carton inner flap is the product code for Abbott Laboratories. The font size is increased for "7.5 mg" on the front panel of the blister card.

     The 2 tablet blister card configuration was not included in the original NDA application dated 12/15/98. A separate CMC amendment will be submitted mid November to support this blister configuration as agreed in the October 6, 1999 telephone conversation.

If you have any further questions, please contact me.

Sincerely,

Alan V. McEmber

Desk Copies: Dr. Sue-Ching Lin Mr. Tony Zeccola

ORIGINAL

ORIGINAL

Boehringer Ingelheim

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

ORIG AMENDMENT

D-L

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938

September 21, 1999

RESPONSE TO FDA REQUEST FOR INFORMATION:
Electronic Copy of Draft Labeling (Package Insert)

Dear Dr. Midthun:

Reference is made to a telephone contact dated September 17, 1999 between Dr. Constance Lewin of your Division and me in which Boehringer Ingelheim Pharmaceuticals, Inc., (BIPI), agreed to provide an electronic copy of the draft package insert in MS Word. Reference is made to the amendment dated August 9, 1999, in which BIPI proposed revisions to the "Clinical Trials" and "Warnings" sections of the labeling. Reference is made to the facsimile dated August 11, 1999 from Dr. Constance Lewin in which it was requested that the statements, "keep in dry place" and "dispense in tight container" be added to the package insert. Final reference is made to the facsimile dated September 9, 1999 in which BIPI provided updated wording in the following sections (Carcinogenicity, Mutagenesis, Impairment of Fertility; Pregnancy; and Labor and Delivery). An official copy of the September 9, 1999 facsimile is attached to this cover letter and is now officially submitted to the NDA.

Please find attached a paper copy and an electronic copy of the annotated and unannotated package insert. The package insert is the same as the version submitted in the July 30, 1999 version, except for editorial changes and the addition of the revised wording made to the labeling sections noted in the above August 9, 1999, August 11, 1999, and September 9, 1999 correspondences.

If you have any further questions, please contact me.

Sincerely:

Alan V. McEmber

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail amcember@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Desk Copy: Dr. Constance Lewin (6)

DUPLICATE

NEW CORRESP

NC

Boehringer Ingelheim

MARTIN KAPLAN, M.D., J.D.
Vice President, Drug Regulatory Affairs

Boehringer Ingelheim Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, Connecticut 06877

September 14, 1999

Dr. Karen Midthun, Acting Director
Division of Anti-Inflammatory, Analgesic,
and Opthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Meloxicam Tablets **General Correspondence**
NDA 20-938

Dear Dr. Midthun:

As a follow-up to our teleconference of September 1, 1999 concerning the intended use by Boehringer Ingelheim Pharmaceuticals, Inc.,(BIPI) of data from our standardized GI endpoint analysis, submitted August 9, 1999, we thought that it might be helpful for us to respond to several concerns that were raised by the Division during this discussion. Of primary importance, please note that BIPI accepts that the labeling for meloxicam should include the standard NSAID PUB warning statement. Our request is that we be allowed to disclose to physicians and patients relevant information concerning the specific PUB risk associated with meloxicam treatment. Outlined below are some limitations of the meloxicam clinical trial database noted by Dr. Hyde along with BIPI responses.

(1) absence of significant endoscopic data differentiating meloxicam from reference NSAIDs

BIPI acknowledges that the meloxicam NDA contains very limited endoscopic data. However the agency agreed with BIPI that clinical outcome data are more relevant in defining PUB risk than endoscopy. In this regard there is extensive clinical trial experience documented with meloxicam.

(2) absence of long-term patient exposure data on meloxicam

BIPI noted that the meloxicam standardized GI endpoint analysis included over 1,000 patients receiving meloxicam 15 mg for at least 6 months and over 500 patients for at least one year. While the substantial majority of patients on 7.5 mg were exposed to only 4 weeks of treatment, it is generally accepted that the hazard rate for PUB development does not increase over time. We agree with the agency that additional long-term clinical experience

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with 7.5 mg would be useful and are willing to discuss options such as a Phase IV clinical outcome study to meet this end.

(3) inability to escalate the dose of meloxicam

The Division noted that the safety margin for meloxicam appears to be relatively narrow. Patients commonly employ higher NSAID doses (e.g., in the treatment of rheumatoid arthritis) and the incremental risk associated with higher dosing is a concern. The Division questioned as to what meloxicam dose is being recommended by BIPI in RA. BIPI indicated that both the 7.5 mg and 15 mg doses are effective in RA and that meloxicam labeling could specifically discourage use of doses higher than 15 mg.

If deemed helpful to the Division, BIPI would be happy to have additional discussions on the inclusion of specific meloxicam PUB risk information in the product labeling. For example, we certainly would consider a commitment to perform a large prospective Phase IV clinical outcome trial to further confirm the results of the standardized GI endpoint analysis.

Once again, we appreciate the enormous efforts being made by the Division in reviewing the massive meloxicam NDA and look forward to a successful completion of the review in the near future.

Sincerely,

Martin M. Kaplan, M.D., J.D.
Vice President, Drug Regulatory Affairs

ORIGINAL

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

ORIG AMENDMENT

BP

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

September 14, 1999

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938

Alan McEmber
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RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

Dear Dr. Midthun:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc.(BIPI) in which specific concerns by the pharmacology reviewer, Dr. Josie Yang were discussed. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Raymond Stoll and myself in which BIPI agreed to revise the NDA toxicology reports to address Dr. Yang's concerns. Final reference is made to the teleconference of July 12, 1999, in which BIPI committed to complete and submit the revised reports by September 16, 1999. The purpose of this letter is to indicate that BIPI now has completed the submission of the last report to the NDA.

In summary, based on the discussions in the May 24, 1999 meeting, the toxicology and preclinical ADME departments assessed the reports submitted in the NDA. Reports were classified into three categories: (1) reports that required revised text, tables, and figures because of data presentation/legibility issues; (2) reports that benefited from the addition of an executive summary [original reports were felt to be acceptable for content, data presentation and legibility as written]; and (3) other reports that are either special toxicology studies conducted on non-oral formulations (e.g., IM/IV), or reports that the sponsor believed were acceptable for content, data presentation and legibility in

Boehringer Ingelheim

RESPONSE TO FDA REQUEST FOR INFORMATION:
Revised Toxicology Reports

the NDA and did not require report revisions or executive summaries to be created.

A total of 53 reports are in category 1 or 2. Of these, 31 revised reports (category 1) and 22 executive summaries attached to the original report (category 2) have been submitted to the NDA. In addition, BIPI submitted an improved copy of one repeat-dose toxicity study. Please see attachment 1 for the list of the reports resubmitted to the NDA.

For ease of review of the submissions, attachment 2 provides a copy of the modified table of contents for Section 5 which updates the location/submission date of each technical report.

BIPI appreciates the efforts made by Dr. Josie Yang to complete the review of such a large number of reports. If there are any additional questions and concerns, please do not hesitate to contact us.

If you have any further questions, please contact me.

Sincerely:

Alan V. McEmber
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

ORIGINAL

Boehringer Ingelheim

Karen Midthun, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

September 13,1999

Re: **Mobic® (meloxicam) 7.5 mg Tablets**
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION
Copies of Published Literature – Section 5

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Dear Dr. Midthun:

We have reviewed the published literature submitted in the Preclinical Section 5 of our NDA 20-938, and have obtained improved copies of the literature cited in the attached Table of Contents.

The improved copies of published literature for Section 5 of the NDA are enclosed and are arranged in the same order in which they were previously submitted in Amendment to NDA 20-938 on February 4, 1999.

If you have any questions, please contact me.

Sincerely,

Alan V. McEmber
Senior Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

Telefax

Boehringer Ingelheim

Ms. Leslie Vaccari
FDA - DAAODP
301.827.2538
301.827.2531

Page 1 of 1

Boehringer Ingelheim
Pharmaceuticals Inc.

April 13, 2000

Confirmation of Final Approved Labeling

Jeffrey R. Snyder
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jsnyder@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Leslie;

By way of this facsimile, BIPI is confirming our receipt and acceptance of the final wording and attached labeling provided in the approval letter for the Mobic® (meloxicam) Tablets, 7.5 mg NDA 20,938, dated April 13, 2000.

Please let me know if any additional information is required.

Sincerely,

Jeffrey R. Snyder
Associate Director

cc: Original NDA 20-938
HFD-550/Div File
/LVACCARI

*** TOTAL PAGE.01 ***

Telefax

Boehringer Ingelheim

Mr. Tony Zeccola
FDA - DAAODP
301-827-2147
301-827-2531

Boehringer Ingelheim
Pharmaceuticals Inc.

April 13, 2000

Confirmation of Changes to Mobic Label

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Ridgefield, CT 06877-0368

Dear Tony;

BIPI accepts the Division's suggested wording for the Mobic® label conveyed in the facsimile dated April 13, 2000 (2 pm) and has incorporated the changes in the draft label. A copy of the final draft label is attached.

BIPI has made no additional changes to the proposed labeling.

Please let me know if any additional information is required.

The formal submission to the NDA will be sent via FedEx today to arrive tomorrow.

Sincerely,

Jeffrey R. Snyder
Associate Director

cc: Original 20-938
HFD-550 Div File
ILVaccari

Telefax

Boehringer Ingelheim

Ms. Leslie Vaccari
FDA - DAAODP
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Boehringer Ingelheim
Pharmaceuticals Inc.

April 13, 2000

Confirmation of Changes to Mobic Label

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900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Leslie;

BIPI accepts the Division's suggested wording for the Mobic® label conveyed in the facsimile dated April 12, 2000 and has incorporated the changes in the draft label. BIPI has made no additional changes to the proposed labeling.

Please let me know if any additional information is required.

The formal submission to the NDA will be sent via FedEx today to arrive tomorrow. A draft of the submission cover letter is attached for reference.

Sincerely,

Jeffrey R. Snyder
Associate Director

cc: Original NDA 20-938
HFD-550 /Div File
/LVACCARI

Boehringer Ingelheim

Karen Midthun, M.D., Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

April 13, 2000

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938
Response to FDA Request for Information

Dear Dr. Midthun:

Martin M. Kaplan, M.D., J.D.
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Reference is made to a facsimile dated April 12, 2000 from Ms. Leslie Vaccari which described changes requested by the Division to the Clinical Trials and Drug Interactions (Warfarin) sections of the Mobic® labeling.

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) agrees with the suggested changes provided in the Agency's facsimile sent April 12, 2000 and has incorporated the changes in the attached copies of the final draft label. BIPI has made no additional changes to the label other than those suggested by the Division.

This submission includes the following attachments:

Package Insert
- Final Draft Package Insert with changes highlighted
- Final Draft Package Insert
- Diskette of Final Draft Package Insert

Please contact me if you require any additional information.

Sincerely,

Martin M. Kaplan, M.D., J.D.
Vice-President
Drug Regulatory Affairs

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Boehringer Ingelheim

Ms. Leslie Vaccari
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Boehringer Ingelheim
Pharmaceuticals Inc.

April 13, 2000

Mobic Final Labeling

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Dear Leslie;

Here is a fax copy of the final labeling, as discussed earlier. Please let me know if you have any questions or comments regarding the fax.

Sincerely,

Jeffrey R. Snyder
Associate Director

Rec'd
APR 13 2000

cc. Original NDA 20-938
HFD-550 LDiv FILE
/LVaccari