

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-584/S003

CORRESPONDENCE

Division Director's Memorandum - NDA 20-584

NDA 20-584

Review date: 7/1/96

Applicant: Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, Pennsylvania 19101-8299

Drug: Lodine XL (etodolac extended release tablets)

Proposed Indication: Management of the signs and symptoms of signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA).

Related Reviews: Medical Officer Review draft dated 6/23/96
Statistical Reviews dated 1/22/96 & 5/23/96
Pharm/Tox Reviews dated 7/17/95 & 3/19/96
Chemistry Review dated 5/29/96
Biopharm Review dated 3/12/96

Background:

The application as submitted, requested approval for the management of the signs and symptoms of osteoarthritis. Following the completion of the review of the rheumatoid arthritis claims in Supplements 13, 14 and 15 of NDA 18-922 (Lodine (etodolac capsules), the applicant revised the labeling to include the rheumatoid arthritis claims.

The proposed dose of Lodine XL was 600 mg to 1200 mg once daily as two or three 400 mg tablets taken together, or one or two 600 mg tablets taken together (for both OA and RA).

Based on the currently approved labeling, "the recommended starting dose of LODINE for the management of the signs and symptoms of osteoarthritis or rheumatoid arthritis is: 300 mg b.i.d., t.i.d., or 400 mg b.i.d., or 500 mg b.i.d. During long-term administration, the dose of LODINE may be adjusted up or down depending on the clinical response of the patient. A lower dose of 600 mg/day may suffice for long-term administration. In patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. When treating patients with higher doses, the physician should observe sufficient increased clinical benefit to justify the higher dose. Physicians should be aware that doses above 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

In chronic conditions, a therapeutic response to therapy with LODINE is sometimes seen within one week of therapy, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required."

NDA 20-584 Lodine XL (etodolac extended release tablets)

Bioequivalence: (from the Pharmacokinetics Review)

The bioequivalence of the test formulations of the extended release of etodolac and the proposed market formulations was established in study 654-C-117-US.

Equivalence (based on AUC) between Lodine XL and conventional etodolac given in 1200 mg total daily doses of 3x400 XL tablets q.d., and 2x200 mg conventional capsules t.i.d. was demonstrated in study 654-C-114-U.S. Bioequivalence was demonstrated between equivalent doses of the 400 mg XL tablet (3x400) and the 600 mg XL tablet (2x600) in this study.

Comments: *Revised dissolution specifications have also been identified and are listed as a deficiency at the end of this review.*

Clinical Review:

A draft review of the clinical data has been completed. The review recommends limited approval for osteoarthritis at a dose level of 400 mg to 600 mg once daily. The medical officer recommends these limitations because of a limited safety data base for the 800 mg and 1200 mg. The rheumatoid arthritis claim was not completely reviewed because the applicant did not originally request this indication.

Comments:

Rheumatoid Arthritis Claim:

The rheumatoid arthritis claim is supported by the bioequivalence of Lodine and Lodine XL. Study 654-D-320 (6-week, multicenter, double-blind, parallel group [400 XL vs 600 XL vs 200 mg bid], rheumatoid arthritis) demonstrated equivalence between each of the doses with respect to Investigator global and patient global. Equivalence was not established based on joint pain count and swollen joint count because of wide confidence intervals. -The strength of the study has been questioned because of the low dose tested and the wide confidence intervals for the joint counts. These issues however are not sufficient to disqualify the indication as discussed with Dr. Weintraub (Office Director, ODE V).

Comments:**Dosage:**

Studies have been conducted with the 400 mg, 600 mg, 800 mg and 1200 mg dosages, however only a limited number of patients have completed 6 months (15 patients at 800 mg and 10 patients at 1200 mg) of therapy. A total of 123 patients of the 800 and 1200 mg groups combined completed 24 weeks.

There were no significant differences between each of the doses studied with respect to efficacy 400-1200 mg.

Based on the assumption that at least 100 patients have successfully completed treatment for 24 weeks at a dose of at least 800 mg. It is recommended that the 800 mg tablet be permitted. Since the majority of studies were performed with the 400 mg and 600 mg qd dose, and the general recommendation for NSAIDs is to treat with the lowest effective dose, the starting dose should be 400 mg to 600 mg.

In the absence of good clinical trials in the 1200 mg immediate release, the inability of patients to tolerate the 1600 mg immediate release, the small number of patients completing the extended release trials and the lack of a dose response for efficacy, it is difficult to justify higher doses of Lodine XL or to establish a threshold for safety.

In addition, dosages above 800 mg require combining the 400 mg tablet with the 600 mg tablet. The ability of patients to successfully combine these tablets has not been tested.

Additional safety information is needed to support doses above 800 mg. It is recommended that a large simple GI trial be conducted in doses of 800 mg, 1000 mg and 1200 mg to support any labeling changes and that the Phase 4 studies for the immediate release be completed as soon as possible.

16 *pages of revised draft
labeling have been
redacted from this portion
of the document.*

10. An identification of the meaning of the letters XL in the name of the drug product and a commitment that the letters will not be used in the future to represent any alternative meaning.

/S/

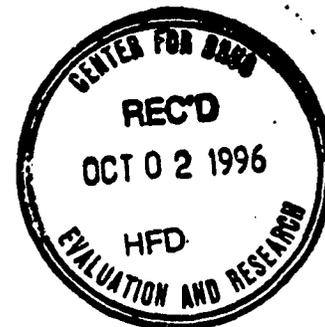
Wiley A. Chambers, M.D.
Acting Division Director

cc: Orig NDA 20-584
HFD-550
HFD-550/Neuner
HFD-550/Yaciw
HFD-550/Leung
HFD-550/Coulter
HFD-550/Chambers

APPEARS THIS WAY
ON ORIGINAL

JOSEPH N BATHISH
Vice-President
Worldwide Regulatory Affairs

October 2, 1996



Lodine® XL
(etodolac extended-release tablets)
NDA No. 20-584

Wiley A. Chambers, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

XL
7/17/96
L

Dear Dr. Chambers:

Reference is made to our pending NDA No. 20-584 for Lodine XL (etodolac extended-release tablets) and to our teleconference with you and Dr. Weintraub on September 27, 1996. During the teleconference you requested that Wyeth-Ayerst submit two additional items and make two post-approval commitments, to allow the Agency to proceed to approval of this application. The two additional items requested are as follows and are enclosed in this submission:

- 1) A copy of the draft package insert (on disk as well as hard copy) for Lodine XL which incorporates the wording for the Dosage and Administration section as previously submitted on September 27, 1996 and agreed to during the teleconference. The other sections of the insert are identical to the FDA July 3, 1996 version that accompanied the Approvable Letter. In addition, the draft container/carton labeling is also attached.
- 2) A final safety update as requested by the Division on September 27, 1996.

In addition, Wyeth-Ayerst also agrees to the following two post-approval commitments:

- Submit 15-day alert reports for all serious gastrointestinal adverse events (labeled and unlabeled) occurring at all doses of Lodine XL. These reports will be submitted to both the Anti-Inflammatory, Analgesic and Ophthalmic Drug Products Division and the Division of Epidemiology and Surveillance.

Lodine® XL
(etodolac extended-release tablets)
NDA No. 20-584

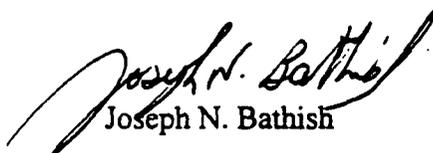
- Provide data from at least 300 patients treated for at least 6 months with 1200 mg/day, to support subsequent approval of a maximum daily dose of 1200 mg/day for Lodine XL. ✓

We understand that all issues relating to the final approval of this NDA have now been addressed, and we look forward to the expeditious approval of this application.

Please contact me at (610) 902-3700 should you have any questions regarding this submission.

Sincerely,

WYETH-AYERST LABORATORIES


Joseph N. Bathish

NEH:jad:865
cc: Dr. Weintraub

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WYETH-AYERST  RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

November 11, 1997

NDA #20-584
Lodine™ XL (etodolac extended release tablets)

Supplement for 1200 mg/day -
Completion of Post-Approval
Commitment



John Hyde, MD, Deputy Director
Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane - Document Control Room
Rockville, MD 20857-1706

20584 003
SE 2

Dear Dr. Hyde:

Reference is made to our approved NDA No. 20-584 for Lodine XL (etodolac extended release tablets). Further reference is made to our letter dated October 17, 1996 in which Wyeth-Ayerst made a post-approval commitment to submit safety data from 300 patients receiving 1200 mg/day of Lodine XL for at least 6 months.

The purpose of this Supplemental New Drug Application is to provide the data necessary to support increasing the maximum daily dose recommended in the labeling of Lodine XL to 1200 mg/day, and to fulfill the above-referenced post-approval commitment. In support of this request, this supplement includes safety and efficacy data on 2,084 patients who have received 800-1200 mg/day of etodolac extended release for at least 2 weeks, 847 patients for at least 6 months and 584 patients for at least one year. Some patients received these doses for as long as 30 months.

From a historical perspective, the Lodine XL development program was conducted to support labeling for the same dosage range approved for the immediate release product in the original Lodine NDA. Therefore, the Lodine XL NDA, when initially submitted on March 31, 1995, included draft labeling which reflected a maximum daily dose of 1200 mg/day (consistent with the approved labeling then in effect for Lodine). During the NDA review, the Agency determined that the maximum approvable dose for Lodine XL would be the same as that approved on October 21, 1996 for the revised conventional release Lodine labeling, 1000 mg/day, rather than that approved in the original NDA for Lodine. Unlike the immediate release dosage form, however, the presently approved labeling for Lodine XL does not contain the

option to increase the maximum daily dose to 1200 mg if a higher level of therapeutic activity is required.

As you may recall, the Lodine immediate release NDA was originally approved in January 1991 with labeling permitting a maximum daily dose of 1200 mg/day. During the review of the Lodine Supplemental NDA approved on June 28, 1996 to add the indication for use in rheumatoid arthritis, the FDA lowered the usual maximum daily dose for Lodine to 1000 mg/day; but the labeling included a provision that for patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. The lowering of the usual maximum daily dose to 1000 mg was not related to increased safety concerns.

In labeling discussions that took place during the original NDA review with the Division regarding Lodine XL, Wyeth-Ayerst inquired what data would be required to support dosage recommendations for a maximum dose of 1200 mg/day. We were informed by Dr. Wiley Chambers (confirmed by Wyeth-Ayerst in our letter dated September 27, 1996) that safety data from at least 300 patients who received 1200 mg/day for at least 6 months would be required to support a maximum daily dose of 1200 mg. Therefore, Wyeth-Ayerst has included in this sNDA safety and efficacy data for 475 patients who received a predominant daily dose of Lodine XL 1200 mg for at least 6 months, and 313 patients who received it for at least 1 year. These data show that in general, the safety profile utilizing the 1200 mg dose is similar to the safety profile characterized in our current approved labeling.

This sNDA includes Item 2 - Application Summary, Item 3 Chemistry, Manufacturing and Controls - Environmental Assessment, Item 4 - Labeling, Item 6 - Human Pharmacokinetics and Bioavailability, Item 8 - Clinical Data Section and Item 10 - Statistical Section, as well as the relevant case report forms and tabulations. The Supplemental NDA consists of 327 Volumes.

Also included as required under the Generic Drug Enforcement Act of 1992 is the certification which is contained in Item 15 of this application. A check for 50% of the required Application Fee [redacted] has also been submitted as appropriate.

Finally, as stated above, Wyeth-Ayerst agreed to a post-approval commitment at the time of NDA approval, to provide the Division with data from 300 patients who received Lodine XL 1200 mg/day for 6 months by the fourth quarter, 1997. This sNDA fulfills this post-approval commitment.

NDA # 20-584
Lodine™ XL (etodolac extended release tablets)

November 11, 1997
Page 3

If you have any questions concerning this application, please contact our representative,
Mr. James O'Shaughnessy at (610) 902-3761.

Sincerely,

WYETH-AYERST LABORATORIES



Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs

NEH:jad:1041.doc

**APPEARS THIS WAY
ON ORIGINAL**

WYETH-AYERST **W** RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

January 21, 1998

NDA No. 20-584/S-003
Lodine® XL (etodolac extended-release tablets)

John E. Hyde, M.D., Ph.D., Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
7701 Corporate Blvd.
College Park, MD 20850

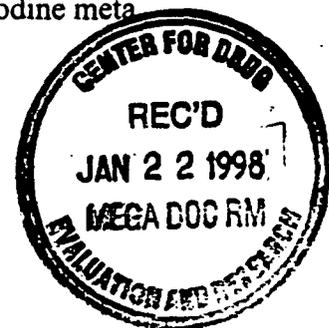
Dear Dr. Hyde:

Reference is made to Wyeth-Ayerst's approved NDA No. 20-584 for Lodine XL (etodolac extended-release tablets) and to our November 11, 1997 submission (S-003) providing information to support increasing the maximum daily dose of Lodine XL tablets to 1,200 mg.

Reference is also made to the January 20, 1998, telephone conversation between Ms. Nancy Holston of Wyeth-Ayerst and Ms. Chin Koerner of the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products regarding Lodine XL supplemental application 003 and other matters. During that teleconference, Wyeth-Ayerst was asked to submit electronic (diskette in ASCII format) pharmacodynamic analyses data relative to the 1,200 mg maximum daily dose supplement.

The purpose of this letter is to provide the attached duplicate diskettes (two), which provide the following electronic files (Attachment 1).

LODINE.DAT	Pharmacodynamic data for indirect response model of Lodine meta analysis.
	Rows 1-14: 100 mg dose
	Rows 15-28: 200 mg dose
	Rows 29-42: 400 mg dose
	Column 1 is time; Column 2 is mean PAIN



John E. Hyde, M.D., Ph.D.
Lodine® XL Tablets
NDA 20-584/S-003
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Page 2 of 2

PID13_IN.DAT Pharmacodynamic data for indirect response model of Lodine XL analysis.

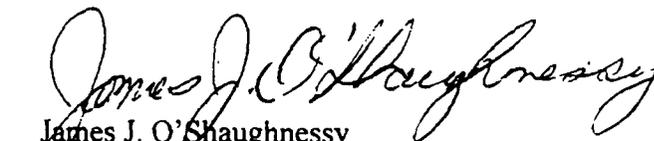
Rows 1-20: 400 mg dose
Rows 21-40: 1,200 mg dose
Column 1 is time; Column 2 is mean PAIN

Attachment 2 contains a paper copy of the electronic data.

We trust that you will find this amendment satisfactory and that Lodine XL supplemental application 003 will be approved at your earliest convenience. If you have any questions concerning this amendment, please contact the undersigned at (610) 902-3761.

Sincerely,

WYETH-AYERST LABORATORIES


James J. O'Shaughnessy
Associate Director
U.S. Regulatory Affairs

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

April 9, 1998

DUPLICATE

NDA No. 20-584/S-003
Lodine® XL (etodolac extended-release tablets)

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



Dear Dr. Weintraub:

Reference is made to Wyeth-Ayerst's approved New Drug Application No. 20-584 for Lodine® XL (etodolac extended-release tablets) and to our November 11, 1997 submission (S-003) providing information to support increasing the maximum daily dose of Lodine® XL tablets to 1,200 mg.

Reference is also made to an April 6, 1998 telephone conference between the following representatives of Wyeth-Ayerst and the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP) to discuss the population pharmacokinetic analysis submitted as part of the Lodine XL supplemental application 003.

Wyeth-Ayerst

Joan Korth-Bradley, Ph. D.
Joseph Boni, Ph. D.
James O'Shaughnessy

DAAODP

Dennis Bashaw, Ph. D.
Vaneeta Tandon, Ph. D.
Chin Koerner

Michael Weintraub, M. D.
Lodine® XL Tablets
NDA 20-584/S-003
April 9, 1998
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During that telephone call, Dr. Tandon pointed out that in the NONMEM data set several patients had apparently received a second dose of Lodine XL eight hours after the first dose. There were no provisions in the study protocol for a second dose of extended-release etodolac which called into question the results of the analysis. Dr. Bashaw remarked that concentrations seemed to rise in these patients which would be consistent with a second dose. It was agreed that Wyeth-Ayerst would examine the data set, make corrections if justified and then repeat the pharmacokinetic and pharmacodynamic analysis if necessary.

The purpose of this submission is to amend supplement 003 to provide a report on the results of our reevaluation of the extended-release etodolac population pharmacokinetic analysis previously provided to the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products.

Our investigation revealed that there were errors in the data set, but the pharmacokinetic and pharmacodynamics results remain largely the same when the correct data set is used.

The case report forms were reviewed as were the randomization tables. Each of the patients affected was shown to have received a second dose of medication from a bottle that contained placebo. No protocol violations were detected. Examination of the SAS program used to prepare the NONMEM data set contained an error that inadvertently input a dose to all of the patients receiving Lodine XL who remained in the study until the 10 hour observation point. The code was corrected and the doses removed. The concentration observations were verified from the assay report and the case report forms as being correct for date, time and concentration as NONMEM data set appeared in the original. Dr. Bashaw's observation that concentrations rose between the 6 and 10 hour observations is actually consistent with the knowledge of the extended-release properties of Lodine XL. Maximum plasma concentrations after Lodine XL administration are observed 6.9 ± 3.3 hours after dose administration.

Working with the corrected NONMEM data set, the population pharmacokinetic analysis was repeated and as shown in Table 1 (Attachment 1). It resulted in a difference in the estimate of volume of distribution. All other parameters were very similar to what was originally reported. The corrected data set is enclosed on a disc and the details are shown in the appendix enclosed as Attachment 2.

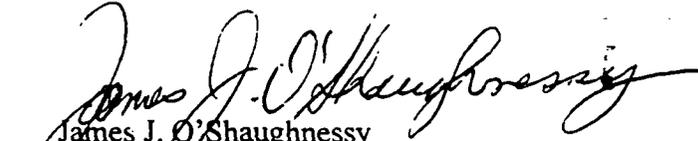
With the new pharmacokinetic parameters, a concentration time profile was generated as before and used with pharmacodynamic data that was previously provided to the reviewers, but is also included here as Attachment 1. As shown in Table 2, the pharmacodynamic results were modestly changed, but unlikely to be of clinical consequence in that the estimate of IC50 remained almost exactly the same. Therefore, the PK and PD arguments originally made in supplement 003 are believed to be still valid.

Michael Weintraub, M. D.
Lodine® XL Tablets
NDA 20-584/S-003
April 9, 1998
Page 3 of 3

We trust that you will find this amendment satisfactory and that Lodine XL supplemental application 003 will be approved at your earliest convenience. Should you have any questions concerning this amendment, please contact the undersigned at (610) 902-3761, or our representative Mr. Dennis Ahern at (610) 902-3791.

Sincerely,

WYETH-AYERST LABORATORIES


James J. O'Shaughnessy
Associate Director
U.S. Drug Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

WYETH-AYERST



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SE2-003
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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

April 21, 1998

NDA No. 20-584/S-003
Lodine® XL (etodolac extended-release tablets)

~~ORIGINAL~~

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



Dear Dr. Weintraub:

Reference is made to our approved New Drug Application No. 20-584 for Lodine® XL (etodolac extended-release tablets) and to our November 11, 1997 submission (S-003) providing information to support increasing the maximum daily dose of Lodine® XL tablets to 1,200 mg.

Reference is also made to an April 3, 1998, telephone conversation between the undersigned and Ms. Chin Koerner, Project Manager, of the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP) regarding clinical information provided in Lodine XL supplemental application 003. During that telephone call, Wyeth-Ayerst was asked to submit patient identification numbers for study subjects meeting the following criteria.

Supportive Tables from the November 11, 1997 Submission

Volume 77: Table 5.5

Volume 78: Tables 5.A, 5.B, and 5.C

Only study subjects with the following reported treatment-emergent study events.

Duodenal Ulcer
Esophageal Ulcer
Intestinal Ulcer
Stomach Ulcer

Intestinal Perforation
Intestinal Bleeding
Intestinal Obstruction
Melena

Michael Weintraub, M.D.

Lodine® XL Tablets

NDA 20-584/S-003

April 21, 1998

Page 2 of 3

On April 8, 1998 the DAAODP telephoned to request that Wyeth-Ayerst provide additional patient ID numbers (Figure 5.1 on page 58 of Volume 77) for study subjects covered by the November 11, 1997 original submission for supplement 003.

The purpose of this submission is to amend supplement 003 to provide the enclosed tables which provide patient identification numbers and information for the study subjects reporting the treatment-emergent study events identified by the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products.

Attachment 1 is a list of patients by identification number with the COSTART study event terms referenced on page one of this letter. Please note that our original submission used the COSTART term "gastrointestinal hemorrhage," not "intestinal bleeding."

This listing separates patients by the study segment in which they presented, and by daily dose. In the double-blind segment, the dose, etodolac ER 800 mg QD or 1200 mg QD, represents the dose to which the patient had been randomized. In the open-label segment, the dose, etodolac ER 800 mg QD or 1200 mg QD, represents the predominant dose that the patient received in the open-label segment. In order to determine a patient's predominant daily dose, the number of days a patient was on either of the alternative dose regimens (800 mg QD vs. 1200 mg QD) was counted and the daily dose with the maximum number of days was used to assign a predominant daily dose to a patient (Vol. 77, page 2).

Two patients, #37017-0012 and #37003-0007, that are included are not counted in Supportive Tables 5.A, 5.B, and 5.C (Vol. 78). These patients had study events that had been reported to Wyeth-Ayerst before the database cut-off deadline, but data was not complete at that time and they were not included in the database. However, these patients were included in the narratives of patients with upper gastrointestinal PUBs, Table 5.9A (Vol. 77, pages 52 - 55) and calculations for the life table presentation of gastrointestinal perforations, ulcers and bleeds (PUBs) (Vol. 77, page 58).

Patients #32309-0009 and #32314-0011 are included in a separate table because they are included in the exposure tables: Volume 77, Table 5.5 and Volume 78, 5.A. These two patients had study events in the double-blind portion of study 0654D-323-US which was included in the original new drug application (NDA 20-584) and in the final GMR (#24720) of the study in the present supplement. These patients are not included in the tables of study events for double-blind study segments in the present submission, because no patients from the 323 double-blind study segment with any study events were included in any of the pooled data from the double-blind study segments reported in S-003. This is because the 323 double-blind segment was of longer duration, 24 weeks, than the segments of the presently other double-blind studies, 4 weeks, and it was felt that it would not be appropriate to pool them together. However, all patients with any study event in the 323 double-blind study segment were included in the overall exposure tables of this supplement, as described on Vol. 77, page 2.

Michael Weintraub, M.D.
Lodine® XL Tablets
NDA 20-584/S-003
April 21, 1998
Page 3 of 3

Attachment 2 is a listing of the narratives of patients with study events under the COSTART terms identified on the first page of this letter.

Attachment 3 is a table with identification number for all patients with upper GI PUBs as presented in the life table analysis in Vol. 77, page 58.

We trust that you will find this amendment satisfactory and that Lodine XL supplemental application 003 will be approved at your earliest convenience. Should you have any questions concerning this amendment, please contact the undersigned at (610) 902-3761, or our representative Mr. Dennis Ahern at (610) 902-3791.

Sincerely,

WYETH-AYERST LABORATORIES



for

James J. O'Shaughnessy
Associate Director
U.S. Drug Regulatory Affairs

WYETH-AYERST **W** RESEARCH

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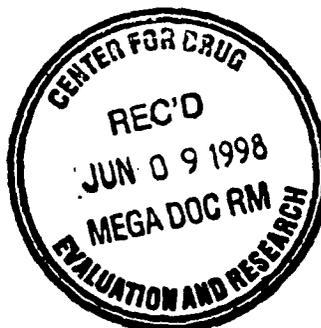
S REGULATORY AFFAIRS

June 8, 1998

NDA No. 20-584/S-003
Lodine® XL (etodolac extended-release tablets)

Noted
6/12/98
WITTER

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



Delivered via Overnight Express

Dear Dr. Weintraub:

Reference is made to Wyeth-Ayerst's approved New Drug Application No. 20-584 for Lodine® XL (etodolac extended-release tablets) and to our November 11, 1997 submission (S-003) providing information to support increasing the maximum daily dose of Lodine® XL Tablets to 1,200 mg.

Reference is also made to May 13, 26 and 27, 1998, telephone conversations between Mr. James O'Shaughnessy of Wyeth-Ayerst Research and Ms. Sharon Schmidt and Dr. Lillian Patrician of the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP) regarding clinical information provided in Lodine XL supplemental application 003. During those telephone discussions, Wyeth-Ayerst was asked to submit additional copies of the protocols for the following Lodine XL clinical studies, as well as SAS datasets for study subjects enrolled in the studies.

PROTOCOL NO. 0654D-323-US

**COMPARISON OF THE SAFETY AND EFFICACY OF 2 DOSES OF ETODOLAC
SUSTAINED-RELEASE TABLETS VERSUS CONVENTIONAL ETODOLAC
CAPSULES IN PATIENTS WITH OSTEOARTHRITIS OF THE KNEE**

Michael Weintraub, M.D.
Lodine® XL Tablets
NDA 20-584/S-003
June 8, 1998
Page 2 of 3

PROTOCOL NO. 0654D-357-US

COMPARISON OF THE SAFETY AND EFFICACY OF 2 DOSES OF ETODOLAC
EXTENDED-RELEASE WITH NAPROXEN IN PATIENTS WITH OSTEOARTHRITIS OF
THE KNEE

PROTOCOL NO. 0654D-357-US

DOUBLE-BLIND PLACEBO-CONTROLLED COMPARISON OF THE SAFETY AND
EFFICACY OF 2 DOSES OF ETODOLAC EXTENDED RELEASE WITH NAPROXEN
FOLLOWED BY AN OPEN LABEL EXTENSION WITH ETODOLAC EXTENDED
RELEASE FOR UP TO TWO YEARS IN PATIENTS WITH OSTEOARTHRITIS OF THE
KNEE

PROTOCOL NO. 0654D-358-US

PLACEBO-CONTROLLED COMPARISON OF THE SAFETY AND EFFICACY OF 2
DOSES OF ETODOLAC EXTENDED-RELEASE WITH NABUMETONE IN PATIENTS
WITH OSTEOARTHRITIS OF THE KNEE

PROTOCOL NO. 0654D-370-US

PLACEBO-CONTROLLED COMPARISON OF THE SAFETY AND EFFICACY OF 2
DOSES OF ETODOLAC EXTENDED-RELEASE WITH NAPROXEN IN PATIENTS
WITH OSTEOARTHRITIS OF THE KNEE

PROTOCOL NO. 0654D-371-US

PLACEBO-CONTROLLED COMPARISON OF THE SAFETY AND EFFICACY OF 2
DOSES OF ETODOLAC EXTENDED-RELEASE WITH NABUMETONE IN PATIENTS
WITH OSTEOARTHRITIS OF THE KNEE

Michael Weintraub, M.D.

Lodine® XL Tablets

NDA 20-584/S-003

June 8, 1998

Page 3 of 3

The purpose of this submission is to amend supplement 003 to 1) answer questions posed by Dr. Patrician during the May 13 telephone call, 2) provide additional copies of instructions regarding the completion of Case Report Forms (CRFs) for the referenced studies, 3) provide SAS datasets for study subjects from the aforementioned clinical trials and 4) provide additional copies of the protocols for studies 0654D-323-US, 0654D-357-US (placebo-controlled and open-label phases), 0654D-358-US, 0654D-370-US and 0654D-371-US.

Attachment 1 is a list of the May 13, 1998 questions from Dr. Patrician as well as our responses.

Attachment 2 contains one sample copy of the CRF, with instructions for completing the form, for each of the above referenced studies.

Attachment 3 provides one copy of each of the study protocols for 0654D-323-US, 0654D-357-US (placebo-controlled and open-label phases), 0654D-358-US, 0654D-370-US and 0654D-371-US.

Attachment 4 contains an IOMEGA Zip disk which provides SAS datasets for study subjects enrolled in the referenced Lodine XL Tablet clinical studies.

We trust that you will find this amendment satisfactory and that Lodine XL supplement 003 will be approved at your earliest convenience. Should you have any questions concerning the enclosed information, please contact the undersigned at (610) 902-3761, or our representative Mr. Dennis Ahern at (610) 902-3791.

Sincerely,

WYETH-AYERST LABORATORIES


James J. O'Shaughnessy
Associate Director
U.S. Drug Regulatory Affairs

WYETH-AYERST **W** RESEARCH

O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

S. REGULATORY AFFAIRS

ORIGINAL

October 16, 1998

ORIG AMENDMENT

SE2003/BL

NDA No. 20-584/S-003
Lodine® XL Tablets



John E. Hyde, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

DELIVERED VIA OVERNIGHT EXPRESS

Dear Dr. Hyde:

Reference is made to our approved new drug application (NDA No. 20-584) for Lodine XL (etodolac extended-release tablets) as well as to our November 11, 1997 submission (S-003) providing clinical data to support increasing the maximum daily dose of Lodine XL Tablets to 1,200 mg per day. This supplemental application was filed in response to a post-approval commitment to submit safety data from 300 patients receiving a 1,200 mg daily dose of etodolac extended-release tablets for a minimum of six months.

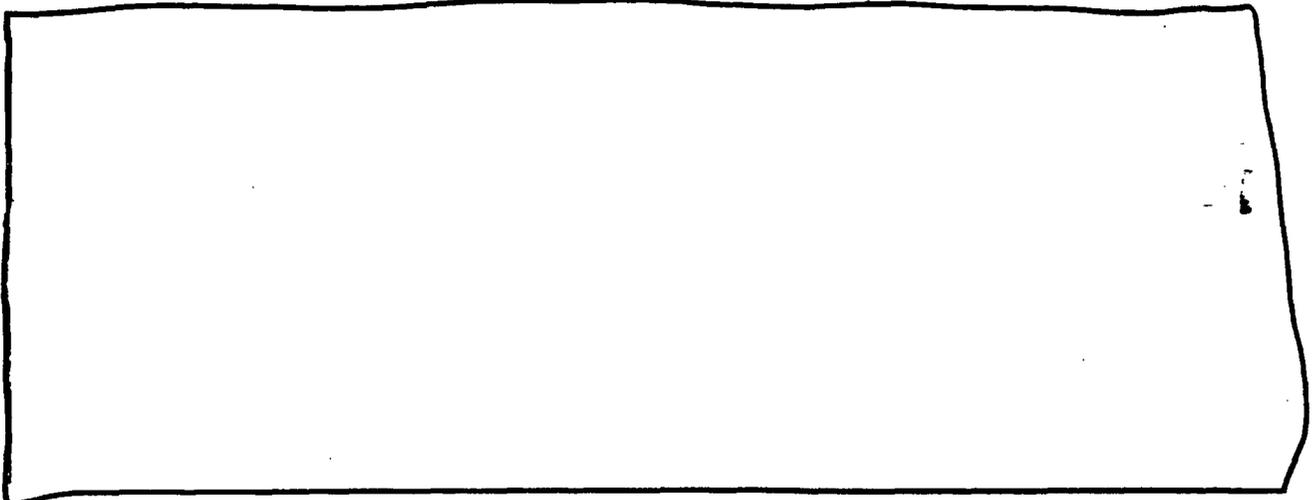
Reference is also made to a September 1, 1998 telephone call from Ms. Chin Koerner of the FDA to our representative Mr. Dennis Ahern relative to Lodine XL supplement 003. Ms. Koerner provided the following preliminary comments on behalf of Dr. James Witter (DAAODP) regarding the draft Lodine XL direction circular filed on November 11, 1997.

- There were no issues regarding the text proposed for the "Dosage and Administration" section.
- The "Clinical Pharmacology" section has been expanded from one to two PK tables. Provide the location of the data to support the changes to Table 1, and the creation of Table 2.

Dr. John Hyde
Lodine® XL Tablets
NDA No. 20-584/S-003
October 16, 1998
Page 2

- There are other text changes (not related to the 1,200 mg dose) between the currently approved product labeling and the draft labeling filed on November 11, 1997. Conduct a side-by-side review of the current and draft labeling. If the changes involve NSAID class labeling or are editorial in nature, they do not require qualification. However, if the proposed revisions are "substantive" in nature, provide an explanation as to where one will find the information to support the proposed text changes.

The purpose of this submission is to respond to the requests made by Ms. Koerner. The following is a listing of the enclosed documents which respond to Ms. Koerner's comments.

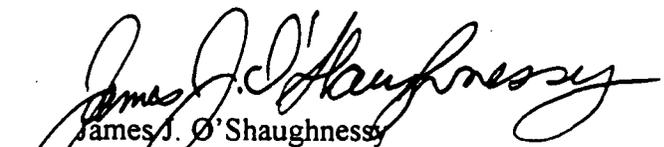


We trust that you will find the enclosed information satisfactory and that Lodine XL supplemental application 003 will be approved at your earliest convenience.

Should you have any questions, please contact the undersigned at (610) 902-3761, or Mr. Dennis Ahern at (610) 902-3791.

Sincerely,

WYETH-AYERST LABORATORIES


James J. O'Shaughnessy
Associate Director
U.S. Regulatory Affairs

WYETH-AYERST  RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

December 7, 1998

NDA No. 20-584/S-003
Lodine® XL (etodolac extended-release tablets)

Response to Approvable Letter:
Revised Labeling

John E. Hyde, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

OVERNIGHT EXPRESS

Dear Dr. Hyde:

Reference is made to our approved New Drug Application No. 20-584 for Lodine® XL (etodolac extended-release tablets) and to our November 11, 1997 submission (S-003) providing information to support increasing the maximum daily dose of Lodine XL Tablets to 1,200 mg.

Reference is also made to your "approvable" letter of November 12, 1998 regarding Lodine XL supplemental application 003 (Attachment 1).

The purpose of this submission is to amend pending supplement 003 to provide revised physician insert labeling. Enclosed you will find a draft copy of the proposed package insert for Lodine XL Tablets (Attachment 2) which has been revised to incorporate the text changes requested in your November 12, 1998 letter. Please refer to page 12 of the draft labeling (page 014 of the attachments). It should be noted that new or changed text has been underlined, while a strikeout has been utilized for deleted text. As requested, the "Dosage and Administration" section has been revised to specify that the initial starting dose of Lodine XL is no more than 1,000 mg per day. A proviso has also been added to permit subsequent dose titration up to a maximum of 1,200 mg per day for individual patients.

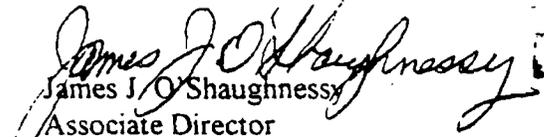
John E. Hyde, M.D., Ph.D., Acting Director
NDA No. 20-584/S-003
Lodine® XL (etodolac extended-release tablets)
December 7, 1998
Page 2

Additionally, the labeling has been clarified to indicate that a dose-response relationship demonstrating greater efficacy above 1,200 mg per day has not been established.

We trust that you will find this amendment satisfactory and that Lodine XL supplemental application 003 will be approved at your earliest convenience. Should you have any questions concerning this amendment, please contact the undersigned at (610) 902-3761, or our representative Mr. Dennis Ahern at (610) 902-3791.

Sincerely,

WYETH-AYERST LABORATORIES


James J. O'Shaughnessy
Associate Director
U.S. Regulatory Affairs

JOS:ag R:DRUGPROD\Lodine.NL:98-020 FDA.doc

**APPEARS THIS WAY
ON ORIGINAL**

WYETH-AYERST  RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

March 24, 1999

NDA No. 20-584/S-003
Lodine® XL (etodolac extended-release tablets)

*Desk Copy for
Ms. Sandra Cook*

John E. Hyde, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

OVERNIGHT EXPRESS

Dear Dr. Hyde:

Reference is made to our approved new drug application No. 20-584 for Lodine XL (etodolac extended-release tablets) and to our November 11, 1997 submission (S-003) providing information to support increasing the maximum daily dose of Lodine XL Tablets to 1,200 mg. This supplement was also submitted to fulfill an October 17, 1996 post-approval commitment made during the review of the original Lodine XL NDA to provide safety data on at least 300 patients treated with a 1,200 mg daily dose of etodolac extended-release tablets for six months.

Reference is also made to the DAAODP's "approvable" letter of November 12, 1998, which advised that supplemental application 003 would be approved after minor revisions were made to the "Dosage and Administration" section of the draft labeling.

On December 7, 1998, Wyeth-Ayerst responded to the November 12 "approvable" letter by forwarding revised draft labeling to incorporate language requested by the FDA to "... specify an initial starting dose of no more than 1,000 mg per day, but with the proviso that the dose may be titrated up to a maximum of 1,200 mg per day in individual patients." Our original draft labeling was further amended as requested by the FDA to "... indicate that a dose response relationship showing greater efficacy at higher doses has not been established." The draft labeling filed on December 7, 1998 complied with each of the text changes requested by the DAAODP on November 12, 1998.

On February 8, 1999, the DAAODP issued a second "approvable" letter for Lodine XL supplement 003. This follow-up letter requested extensive changes to the content and format of the Lodine XL draft labeling provided by the DAAODP on November 12, 1998.

Further reference is made to the March 3, 1999 teleconference between Dr. John Hyde and Ms. Sandy Cook of the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP) and Messrs. Roy Baranello, Jr. and James O'Shaughnessy of Wyeth-Ayerst regarding the Lodine XL draft labeling enclosed with the February 8, 1999 "approvable" letter. The following agreements were reached during this telecommunication.

- Adverse experience terms should only appear in one category (1 - 10%, reported occasionally or occur rarely) of the "Adverse Reactions" section of the labeling. The placement of the terms should be determined by the frequency of the reported AEs.
- Language that appears in the currently approved labeling, but deleted from the February 8, 1999 FDA revision of the draft labeling, may be retained in the Lodine XL package insert.
- The "Adverse Reactions" section of the labeling should reflect Wyeth-Ayerst's clinical trial experience with Lodine XL. Therefore, it is acceptable to distinguish those AE terms listed in the 1 -10% category which were actually reported at a frequency of < 1% in Wyeth-Ayerst clinical trials.

The purpose of this letter is to amend Lodine XL pending supplemental application 003 to provide revised draft labeling which retains a majority of the language suggested in the DAAODP draft of February 8, 1999. The reasons for deviations from the verbiage provided by the DAAODP are outlined in the pages enclosed as Attachment 1. The revised Lodine XL draft labeling is contained in Attachment 2. Attachment 3 provides, for the reviewer's convenience, a copy of the currently approved package insert for Lodine XL Tablets.

In summary, the revised draft labeling enclosed with this letter incorporates most of the changes requested by the DAAODP. We have included explanations where there are differences to accurately reflect our clinical trial data or based on already approved labeling statements.

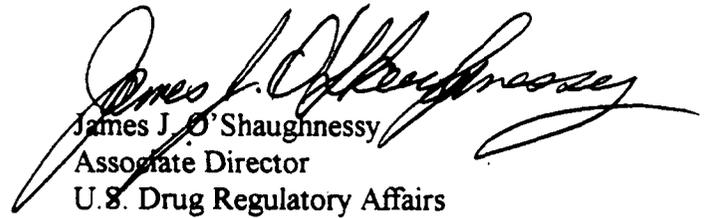
We trust you will find this amendment satisfactory and that Lodine XL supplemental application 003 will be approved at your earliest convenience. We also request that the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products provide formal acknowledgment that we have fulfilled the October 17, 1996 post-approval commitment referenced in the opening paragraph of this letter.

John E. Hyde, M.D., Ph.D., Acting Director
NDA No. 20-584/S-003
Lodine® XL (etodolac extended-release tablets)
March 24, 1999
Page 3

Should you have any questions concerning this amendment, please contact the undersigned at (610) 902-3761, or our representative, Mr. Dennis Ahern at (610) 902-3791.

Sincerely,

WYETH-AYERST LABORATORIES


James J. O'Shaughnessy
Associate Director
U.S. Drug Regulatory Affairs