

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-584/S-005

CORRESPONDENCE

U.S. REGULATORY AFFAIRS

October 12, 1999

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

Douglas L. Sporn, M. D., Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, MD 20855-2773



SUBMISSION OF PEDIATRIC STUDY REPORTS

PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Dear Dr. Sporn:

Reference is made to our approved new drug application (NDA No. 20-584) for Lodine XL (etodolac extended-release tablets) and to the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP), which is the responsible CDER reviewing division for this marketed product.

On February 3, 1999, the Office of Drug Evaluation V issued a "Written Request" letter to Wyeth-Ayerst regarding the conduct a clinical study of etodolac extended-release tablets in juvenile rheumatoid arthritis patients to obtain information on Lodine XL in the pediatric population.

Douglas L. Sporn, M. D.
Lodine® XL Tablets
NDA No. 20-584
October 12, 1999
Page 2

The purpose of this letter is to advise the Office of Generic Drugs that as per the terms specified in the Agency's February 3, 1999 "Written Request" letter (Attachment 1), the results of this study were submitted on October 12, 1999. A copy of our cover letter to the DAAODP is enclosed as Attachment 2.

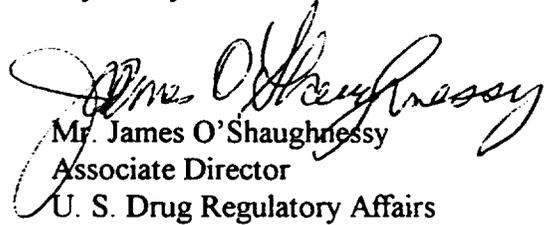
It is Wyeth-Ayerst's expectation that based on this submission, the market exclusivity of Lodine XL will be extended 6 months as per the provisions of Section 505A of the Federal Food, Drug and Cosmetic Act (Section 111 of the FDA Modernization Act of 1997).

We trust you will not grant approval of any pending ANDAs for etodolac extended-release products before confirming with the DAAODP that 6 months of pediatric exclusivity has been granted for Lodine XL, which would extend market exclusivity to April 25, 2000.

If you have any questions regarding this letter, please contact the undersigned at (610) 902-3761, or Mr. Robert Quinty at (610) 902-3789.

Sincerely,

Wyeth-Ayerst Laboratories


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

cc: HFD-550: Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-105: Office of Drug Evaluation V

JOS:jos R:/Lodine XL/Dr. Sporn Letter 10-8-99. doc

WYETH-AYERST  RESEARCH

BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3720
FAX: (610)964-5973

Division of American Home Products Corporation

REGULATORY AFFAIRS

January 31, 2000

NDA No. 20-584/S-005
Lodine® XL Tablets

NDA SUBMITTANCE

SES-005 BM

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



Overnight Express

N.H.
2/14/00
WITTEL

Dear Dr. Midthun:

Reference is made to our approved new drug application (NDA No. 20-584) for Lodine® XL (etodolac extended-release tablets) and to Wyeth-Ayerst's October 12, 1999 submission of a pediatric study report to the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP). That submission was made in response to a February 3, 1999 "Written Request" to Wyeth-Ayerst for the conduct of an etodolac extended-release clinical trial in pediatric patients with juvenile rheumatoid arthritis (JRA). The October 12, 1999 supplemental application (S-005) contained draft copy of the Lodine XL Tablet direction circular, which had been revised to incorporate proposed changes based on the information acquired from the following etodolac extended-release pediatric study.

Protocol No. 0654D1-386-US
Clinical Study Report No. 37670

ORIGINAL

**A 12-WEEK, OPEN-LABEL STUDY OF ETODOLAC ADMINISTRATION IN
PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS,
INCLUDING AN OPTIONAL 8-WEEK EXTENSION**

Karen Midthun, M. D.
Lodine® XL Tablets
NDA No. 20-584/S-005
January 31, 2000
Page 2

On January 7, 2000, Wyeth-Ayerst received a DAAODP facsimile (Attachment 1) with comments regarding the aforementioned etodolac extended-release JRA clinical trial. The purpose of this letter is to provide responses to the January 7 DAAODP comments.

1. Regarding the JRA study recently submitted, please provide a table of the 32 patients who were JRA DOI responders with the 6 JRA DOI criteria listed for each patient and what the values were for each of these criteria at the 4-week endpoint (vs. baseline) selected in this study. In other words, I would like to see what variables improved in these patients that they ended up being considered responders. Please also provide the patients diagnosis, i.e., polyarticular, pauciarticular or systemic JRA.

Wyeth-Ayerst Response

The table enclosed as Attachment 2 contains data for the 32 patients considered JRA DOI responders. This table lists the individual patient numbers, JRA diagnosis and the six JRA DOI criteria at baseline as well as at the 4-week time point.

2. Please review Tables 9.3.1.A – 9.3.1.D (Volume 2 of this submission on October 12, 1999) to confirm that these numbers are correct.

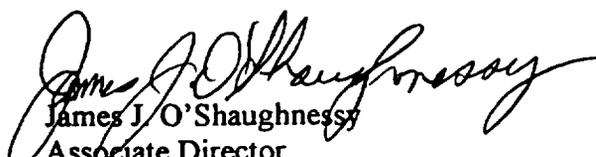
Wyeth-Ayerst Response

The above referenced efficacy tables (Attachment 3) have been verified. One typographical error was discovered on page 51. The mean change from baseline at week 2 was reported as $1.0 \pm .2^*$. It should have reported as $1.0 \pm 2.2^*$.

We trust that you will find the enclosed information satisfactory and that Lodine XL supplement 005 will be approved at your earliest convenience. If you have questions, please contact the undersigned at (610) 902-3761, or Mr. Robert Quinty at (610) 902-3789.

Sincerely,

WYETH-AYERST LABORATORIES


James J. O'Shaughnessy
Associate Director
Worldwide Regulatory Affairs

REGULATORY AFFAIRS



February 28, 2000

NDA No. 20-584/S-005
Lodine® XL Tablets

NDA SUPPL AMENDMENT

Karen Midthun, M. D., Acting Director
Division of Anti-inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

SES-005 BM

Overnight Express

Dear Dr. Midthun:

Reference is made to our approved new drug application (NDA No. 20-584) for Lodine® XL (etodolac extended-release tablets) and to Wyeth-Ayerst's October 12, 1999 submission (S-005) of a pediatric study report to the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP). That submission was made in response to a February 3, 1999 "Written Request" to Wyeth-Ayerst for the conduct of the following etodolac extended-release clinical trial in pediatric patients with juvenile rheumatoid arthritis (JRA).

Protocol No. 0654D1-386-US
Clinical Study Report No. 37670

ORIGINAL

A 12-WEEK, OPEN-LABEL STUDY OF ETODOLAC ADMINISTRATION IN PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS, INCLUDING AN OPTIONAL 8-WEEK EXTENSION

Reference is also made to a February 18, 2000 telephone conversation between Dr. Qian Li and Ms. Sandra Cook of the DAAODP and the undersigned regarding the aforementioned etodolac extended-release JRA clinical trial.

Karen Midthun, M. D.
Lodine® XL Tablets
NDA No. 20-584/S-005
February 28, 2000
Page 2

The purpose of this letter is to provide responses to the February 18 DAAODP requests for additional information regarding the etodolac extended-release JRA clinical trial.

1. The reported number of study subjects listed for the week 2, 4, 8, 12 and 20 visits differ [Tables 9.3.1A – 9.3.1D (Volume 2: pages 046 – 055 of Volume 2 of the submission on October 12, 1999)]. Please explain.

Wyeth-Ayerst Response

Attachment 1 contains an explanation for the number of patients analyzed in the efficacy tables (Tables 9.3.1A – 9.3.1D).

2. Please provide the corresponding SAS data sets for etodolac extended-release tablet Protocol No. 0654D1-386-US.

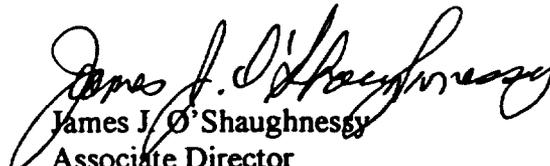
Wyeth-Ayerst Response

Attachment 2 provides a CD containing the SAS data sets relative to the etodolac extended-release tablet JRA clinical trial.

We trust that you will find the enclosed information satisfactory and that Lodine XL supplement 005 will be approved at your earliest convenience. If you have questions, please contact the undersigned at (610) 902-3761, or Mr. Robert Quinty at (610) 902-3789.

Sincerely,

WYETH-AYERST LABORATORIES


James J. O'Shaughnessy
Associate Director
Worldwide Regulatory Affairs

REGULATORY AFFAIRS

NDA No. 20-584/S-005
Lodine® XL Tablets

Ms. Jane Axelrod
Associate Director of Policy
Office of the Center Director, HFD-005
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852



March 21, 2000

NDA 20-584/S-005
BM
565-005

Overnight Express

Dear Ms. Axelrod:

Reference is made to Wyeth-Ayerst's approved new drug application (NDA No. 20-584) for Lodine® XL (etodolac extended-release tablets) and to our October 12, 1999 submission of a pediatric study report to the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP). Attachment 1 is a copy of the October 12, 1999 cover letter for a Lodine XL submission filed in response to a February 3, 1999 "Written Request" from the Office of Drug Evaluation V to Wyeth-Ayerst regarding the conduct of the following etodolac clinical trial in pediatric patients with juvenile rheumatoid arthritis (JRA).

Protocol No. 0654D1-386-US

Clinical Study Report No. 37670

**A 12-WEEK, OPEN-LABEL STUDY OF ETODOLAC ADMINISTRATION IN
PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS.
INCLUDING AN OPTIONAL 8-WEEK EXTENSION**

ORIGINAL

Ms. Jane Axelrod
Lodine® XL Tablets
NDA No. 20-584/S-005
March 21, 2000
Page 2

The October 12, 1999 Lodine XL pediatric exclusivity submission of the JRA study results (Protocol No. 0654D1-386-US) included draft physician insert labeling based on information collected during the etodolac extended-release tablet pediatric study. The October 12, 1999 submission was assigned supplement number 005 by the DAAODP. Attachment 2 is a copy of the draft labeling provided in Lodine XL supplement 005. New verbiage regarding the use of etodolac to treat pediatric patients has been added to the following portions of the Lodine XL physician insert.

“CLINICAL PHARMACOLOGY” section
“Special Populations” subsection
“Pediatric” heading

“CLINICAL TRIALS” section
“Arthritis” subsection

“PRECAUTIONS” section
“Pediatric Use” subsection

Section 103 of the Food and Drug Modernization Act of 1997 speaks to the FDA’s authority to assess and use drug fees. Subparagraph (F) “Exception for supplements for pediatric indications.” reads:

“A supplement to a human drug application proposing to include a new indication for use in pediatric populations shall not be assessed a fee under subparagraph (A).”

The purpose of this letter is to request a refund of the [redacted] user fee payment made previously by Wyeth-Ayerst in support of the October 12, 1999 Lodine XL pediatric labeling supplement (NDA No. 20-584/S-005). Attachment 3 provides documentation for the user fee payment.

Ms. Jane Axelrod
Lodine® XL Tablets
NDA No. 20-584/S-005
March 21, 2000
Page 3

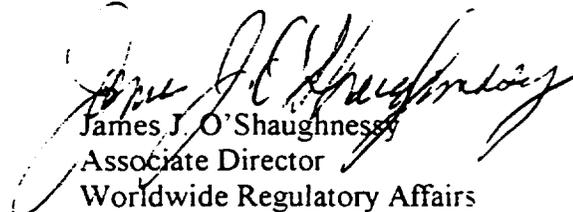
The refund check should be made payable to "Wyeth-Ayerst Pharmaceuticals" and may be sent to the following address:

Wyeth-Ayerst Pharmaceuticals
P. O. Box 8299
Philadelphia, PA 19101-8299
Attn: Mr. James J. O'Shaughnessy, SDC 170/2

If you have questions regarding this communication, please contact me at (610) 902-3761.

Sincerely,

WYETH-AYERST LABORATORIES



James J. O'Shaughnessy
Associate Director
Worldwide Regulatory Affairs

cc: HFD-105: Office of Drug Evaluation V
HFD-550: Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products
HFD-005: Mr. Michael Jones

REGULATORY AFFAIRS

NDA SUPPL AMENDMENT

May 19, 2000

NDA No. 20-584/S-005
Lodine® XL Tablets

Karen Midthun, M. D., Acting Director
Division of Anti-inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850



SES-005 BM

Overnight Express

Dear Dr. Midthun:

Reference is made to our approved new drug application (NDA No. 20-584) for Lodine® XL (etodolac extended-release tablets) and to Wyeth-Ayerst's October 12, 1999 submission (S-005) of a pediatric study report to the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP). That submission was made in response to a February 3, 1999 "Written Request" to Wyeth-Ayerst for the conduct of the following etodolac extended-release clinical trial in pediatric patients with juvenile rheumatoid arthritis (JRA).

Protocol No. 0654D1-386-US
Clinical Study Report No. 37670

**A 12-WEEK, OPEN-LABEL STUDY OF ETODOLAC ADMINISTRATION IN
PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS,
INCLUDING AN OPTIONAL 8-WEEK EXTENSION**

On April 18, 2000, Wyeth-Ayerst received a DAAODP facsimile (Attachment 1) requesting the submission additional clinical information for all of the pediatric patients studied in the aforementioned etodolac extended-release JRA clinical trial.

ORIGINAL

Karen Midthun, M. D.
Lodine® XL Tablets
NDA No. 20-584/S-005
May 19, 2000
Page 2

The purpose of this letter is to provide Wyeth-Ayerst's response to the DAAODP facsimile of April 18, 2000.

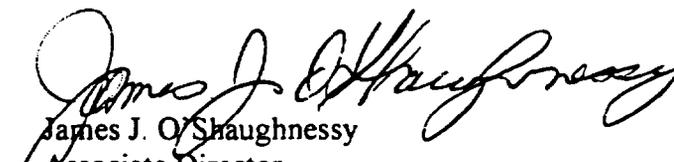
Wyeth-Ayerst Response

The table enclosed as Attachment 2 contains data for the each of the pediatric patients studied in etodolac ER Protocol No. 0654D1-386-US. This table lists the individual patient numbers, JRA diagnosis and the six JRA DOI criteria at baseline as well as at the 4-week time point.

We trust that you will find the enclosed information satisfactory and that Lodine XL supplement 005 will be approved at your earliest convenience. If you have questions, please contact the undersigned at (610) 902-3761.

Sincerely,

WYETH-AYERST LABORATORIES


James J. O'Shaughnessy
Associate Director
Worldwide Regulatory Affairs

U.S. REGULATORY AFFAIRS



July 26, 2000

NDA No. 20-584/S-005
Lodine® XL Tablets

Karen Midthun, M.D., Director
Division of Anti-inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

OVERNIGHT EXPRESS

Dear Dr. Midthun:

Reference is made to Wyeth-Ayerst's approved new drug application (NDA No. 20-584) for Lodine® XL (etodolac extended-release tablets) and to our October 12, 1999 submission (S-005) of a pediatric study report to the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP). That submission was made in response to a February 3, 1999 "Written Request" to Wyeth-Ayerst (W-A) for the conduct of an etodolac extended-release clinical trial in pediatric patients with juvenile rheumatoid arthritis (JRA).

Reference is also made to a July 17, 2000 telephone conversation between Ms. Sandra Cook of the DAAODP and the undersigned regarding the need for the filing of a categorical exclusion statement for Lodine XL supplement 005.

The purpose of this letter is to amend Lodine XL supplemental application 005 to provide the attached environmental assessment statement of compliance. We trust that pending S-005 will now be approved at your earliest convenience.

DUPLICATE

Karen Midthun, M. D., Director
Lodine® XL Tablets
NDA No. 20-584/S-005
July 26, 2000
Page 2

If you have questions, please contact the undersigned at (610) 902-3761.

Sincerely,

WYETH-AYERST LABORATORIES


James J. O'Shaughnessy
Associate Director
Worldwide Regulatory Affairs

WYETH-AYERST **W** RESEARCH

PO BOX 8299 - PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

August 11, 2000

NDA No. 20-584/S-005

Lodine® XL Tablets

Karen Midthun, M.D., Director
Division of Anti-inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Midthun:

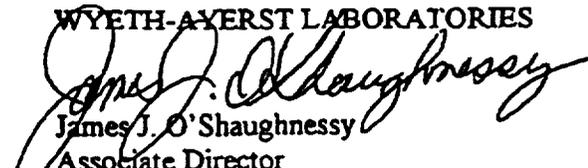
Reference is made to Wyeth-Ayerst's approved new drug application (NDA No. 20-584) for Lodine® XL (etodolac extended-release tablets) and to our October 12, 1999 submission (S-005) of a pediatric study report to the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP). That submission was made in response to a February 3, 1999 "Written Request" to Wyeth-Ayerst (W-A) for the conduct of an etodolac extended-release clinical trial in pediatric patients with juvenile rheumatoid arthritis (JRA).

Reference is also made to an August 9, 2000 facsimile (containing revised labeling) from the DAAODP to Wyeth-Ayerst in relation to the draft physician insert labeling included in the October 12, 1999 pediatric labeling supplemental application (S-005).

The purpose of this letter is to advise you that W-A accepts the proposed labeling supplied by the DAAODP on August 9, 2000. We trust that pending S-005 will be approved at your earliest convenience.

If you have questions, please contact the undersigned at (610) 902-3761.

Sincerely,

WYETH-AYERST LABORATORIES

James J. O'Shaughnessy
Associate Director
Worldwide Regulatory Affairs