

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-584/S-005

ADMINISTRATIVE DOCUMENTS

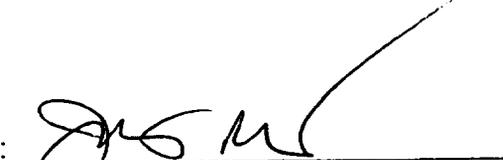
Lodine® XL (etodolac extended-release tablets)

NDA No. 20-584

Certification Required By The Generic Drug Enforcement Act of 1992

Wyeth-Ayerst hereby certifies that it did not, and will not, knowingly use in any capacity the services of any person debarred under subsections (a) or (b) of section 306 of the Federal Food, Drug and Cosmetic Act in conjunction with this supplemental application for NDA No. 20-584 for Lodine XL (etodolac extended-release tablets).

Signed: _____


Mr. Justin R. Victoria
Vice President
Worldwide Regulatory Affairs

Certi/Lodine XL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Wyeth-Ayerst Laboratories

DATE OF SUBMISSION

July 26, 2000

TELEPHONE NO. (Include Area Code)

(610) 902-3761

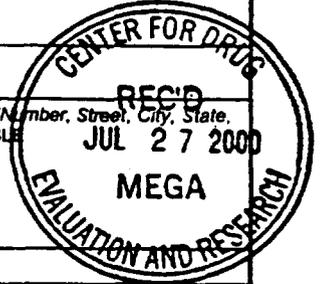
FACSIMILE (FAX) Number (Include Area Code)

(610) 964-5972

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

P.O. Box 8299
Philadelphia, PA 19101-8299

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code telephone & FAX number) IF APPLICABLE



PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA No. 20-584

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Etodolac Extended-Release Tablets

PROPRIETARY NAME (trade name) IF ANY

Lodine® XL

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

(±) 1.8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid.

CODE NAME (if any)

AY-24-235

DOSAGE FORM:

lets

STRENGTHS:

400 mg., 500 mg., 600 mg.

ROUTE OF ADMINISTRATION:

Oral

PROPOSED INDICATION(S) FOR USE:

Indicated for the management of the signs and symptoms of OA and RA.

APPLICATION INFORMATION

APPLICATION TYPE
(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

one

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

- | |
|--------------------------------------------------------------------------------------------------------------------|
| 1. Index |
| 2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling |
| 3. Summary (21 CFR 314.50(c)) |
| 4. Chemistry section |
| A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d) (1), 21 CFR 601.2) |
| B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (I), 21 CFR 601.2) |
| 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2) |
| 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) |
| 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4)) |
| 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) |
| 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2) |
| 10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2) |
| 11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) |
| 12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) |
| 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
| 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A)) |
| 15. Establishment description (21 CFR Part 600, if applicable) |
| 16. Debarment certification (FD&C Act 306 (k) (1)) |
| 17. Field copy certification (21 CFR 314.50(k) (3)) |
| 18. User Fee Cover Sheet (Form FDA 3397) |

19. OTHER (Specify) Environmental Assessment Statement of Compliance

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

James J. O'Shaughnessy

TYPED NAME AND TITLE

James J. O'Shaughnessy, Associate Director

DATE

July 26, 2000

ADDRESS (Street, City, State, and ZIP Code)

P.O. Box 8299, Philadelphia, PA 19101-8299

Telephone Number

(610) 902-3761

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Washington, DC 20201

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Division Director's Memorandum

NDA 20-584
SE5-005

Submission Date: October 12, 1999
Receipt Date: October 12, 1999
Memo Date: July 23, 2000
Applicant: Wyeth-Ayerst Research
Drug Name: Lodine® XL tablets
Generic Name: etodolac extended release tablets
Pharmacologic Category: nonsteroidal anti-inflammatory drug (NSAID)
Proposed Indication: juvenile rheumatoid arthritis (JRA)
Dosage Form and Route: oral tablet, 400 mg, 500 mg, 600 mg
Related Reviews: James Witter, M.D., Ph.D., Medical Reviewer
E. Dennis Bashaw, Ph.D., PK Reviewer

The sponsor has submitted a pediatric study report and revised draft labeling to incorporate pediatric use information, and has requested pediatric exclusivity. This submission is in response to a Written Request by FDA issued February 3, 1999 to obtain needed information on Lodine XL for the treatment of JRA. The Written Request letter requested a 12 week study in at least 68 pediatric patients between 6 and 16 years of age with JRA, with primary objectives to evaluate steady-state pharmacokinetic parameters and the clinical response (safety and efficacy) of the administration of Lodine XL over at least a 12-week period

The current submission includes study report CSR 37670 "A 12-week, open-label study of etodolac administration in patients with juvenile arthritis, including an 8-week optional extension." The pharmacokinetic parameters for the JRA patients treated in this open-label study were compared to pharmacokinetic results from adult rheumatoid arthritis patients from General Medical Report-37835 "Population pharmacokinetic analyses of etodolac in patients with active rheumatoid arthritis and in patients following oral surgery." These reports are reviewed by Drs. Witter and Bashaw. These data are viewed in the context of the Rheumatoid Arthritis Guidance (Guidance for Industry: Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis, issued February 1999). The Guidance notes that for NSAIDs approved for adult rheumatoid arthritis, safety and PK data in JRA patients may be sufficient to extend the indication to JRA (for relief of signs and symptoms, including polyarticular, pauciarticular, and systemic course JRA). Specifically, the Guidance states "For currently approved traditional (cyclooxygenase inhibitor) NSAIDs and corticosteroids, adequate efficacy information exists to support a labeled indication for all JRA and all JRA subset ... For such agents, a labeling claim could be supported using only PK, PD, and safety data in JRA patients, although submission of additional efficacy data is encouraged."

Based on these considerations and the medical officer and PK reviews, the Division recommends that the pertinent pediatric use information be included in the label, and that the Indication section be revised to include the following: "For relief of the signs and symptoms of juvenile rheumatoid arthritis."

15/

Karen Midthun, M.D.
Division Director, DAAODP

C:

NDA 00 384
HFD 350 (D.V. Files)
HFD 350 / Midthun / Goldkind
HFD 350 - /w. Her
HFD 350 / Cook

July 21, 2000

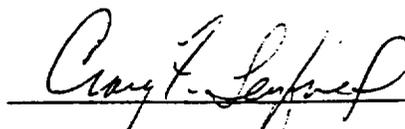
Environmental Assessment

Statement of Compliance

Wyeth-Ayerst Pharmaceuticals states that an Environmental Assessment (EA) for the proposed action on NDA No. 20-584 supplemental application 005, a labeling change relative to the use of Lodine® XL Tablets (etodolac extended-release tablets) to treat pediatric patients with juvenile rheumatoid arthritis, is categorically excluded according to 21 CFR 25.31(b).

The aforementioned regulation states that a categorical exclusion is permitted for "Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion." The Expected Introduction Concentration (EIC) of etodolac is below one part per billion.

To the best knowledge of Wyeth-Ayerst Pharmaceuticals, no extraordinary circumstances exist associated with the proposed action.



Craig F. Seyfried
Senior Director
Environmental Health & Safety
Wyeth-Ayerst Pharmaceuticals