CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-584/S003

APPROVAL LETTER

Div file

NDA 20-584/S-003

MAY 27 1999

Wyeth-Ayerst Research
Attention: James J. O'Shaughnessy
Associate Director, U.S. Drug Regulatory Affairs
P.O. Box 8299
Philadelphia, Pennsylvania 19101-8299

Dear Mr. O'Shaughnessy:

Please refer to your supplemental new drug application dated November 11, 1997, received November 12, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lodine XL (etodolac extended-release tablets) Tablets, 400 mg, 500 mg, and 600 mg. We also refer to our approvable letters of November 12, 1998 and February 8, 1999.

We acknowledge receipt of your submission dated March 24, 1999. Your submission of March 24, 1999, constituted a complete response to our February 8, 1999, action letter.

This supplemental new drug application provides for the use of Lodine XL (etodolac extended-release tablets) Tablets, 400 mg, 500 mg, and 600 mg for management of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-584/S-003." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 3, 2000. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Sandra N. Cook, Project Manager, at (301) 827-2090.

Sincerely,

/S/ 5-27-99

John E. Hyde, Ph.D., M.D.,
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-584/S003

APPROVABLE LETTER

NDA 20-584/S-003

FEB 08 1999

Wyeth-Ayerst Research
Attention: James J. O'Shaughnessy
Associate Director, U.S. Drug Regulatory Affairs
P.O. Box 8299
Philadelphia, Pennsylvania 19101-8299

Dear Mr. O'Shaughnessy:

Please refer to your supplemental new drug application dated November 11, 1997, received November 12, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lodine XL (etodolac extended-release tablets) Tablets. We also refer to our approvable letter of November 12, 1998.

We acknowledge receipt of your submission dated December 7, 1998.

This supplement proposes the following change: increase the maximum daily dose recommended in the labeling of Lodine XL to 1200 mg/day.

We have completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling.

Please submit 20 copies of the printed labels and other labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic

Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Sandra N. Cook, Project Manager, at (301) 827-2090.

Sincerely,

/S/ 2-8-99

John E. Hyde, Ph.D., M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-584/SE2-003

Wyeth-Ayerst Research
Attention: Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs
P.O. Box 8299
Philadelphia, Pennsylvania 19101-8299

NOV 12 1998

Dear Mr. Baranello:

Please refer to your supplemental new drug application dated November 11, 1997, received November 12, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lodine XL (etodolac extended-release tablets) Tablets.

We acknowledge receipt of your submissions dated November 26, 1997; January 21; April 9 and 21; June 8; and October 16, 1998. The user fee goal date for this application is November 12, 1998.

This supplement proposes the following change: increase the maximum daily dose recommended in the labeling of Lodine XL to 1200 mg/day.

We have completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

The labeling should specify an initial starting dose of no more than 1000 mg per day, but with the proviso that the dose may be titrated up to a maximum of 1200 mg per day in individual patients. The labeling should also indicate that a dose response relationship showing greater efficacy at higher doses has not been established.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

I additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options

under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Sandra N. Cook, Project Manager, at (301) 827-2090.

Sincerely,

/S/ 11-12-98

John E. Hyde, Ph.D., M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL