NDA 18-754

S-025

19-816

S-007

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-754/S-025
NDA 19-816/S-007

AUG - 5 1997

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

Dear Mr. O'Shaughnessy:

We acknowledge your supplemental new drug applications dated July 3, 1996, received July 8, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ORUDIS® Capsules (ketoprofen capsules), NDA 18-754/S-025, and ORUVAIL® Extended-Release Capsules (ketoprofen extended release capsules), NDA 19-816/S-007.

The supplemental applications provide for revisions in the ADVERSE REACTIONS sections of the package inserts.

We have completed the review of these supplemental applications and they are approved effective on the date of this letter.

This approval affects only the changes specifically submitted in these supplemental applications. Other changes that may have been approved or are pending evaluation are not affected.

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

We further remind you of our letter dated December 20, 1996, concerning additional recommendations for labeling of non-steriodal anti-inflammatory drug products.

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

Sincerely,

8-5-97

John E. Hyde, M.D., Ph.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

cc:
NDAs 18-754, 19-816
HFD-550/Div. files
HFD-550/Cook
HFD-550/SPMS/LLoBianco 8/5/97
HFD-550/MO/CFang C.F 7/31/97
HFD-105

Drafted by: S Cook/7-31-97/n:\lissa\n18754ap.doc

APPROVAL (AP)

NDA #18-754/S-025
19-816/S-007

LABELING REVIEW OF NDA

NDA 18-754/S-025 **19-816/S-007**	**Submission Date:** **Review Date:**	7/8/96 12/4/96

Drug name:	ORUDIS CAPSULES ORUVAIL Extended-Release CAPSULES
Generic name:	ketoprofen capsules ketoprofen extended-release capsules
Sponsor:	Wyeth-Ayerst Laboratories P.O. Box 8299 Philadelphia, PA 19101-8299 (601) 341-2239
Pharmacologic Category:	Nonsteroidal anti-inflammatory drug (NSAID)
Proposed Indication:	For the management of the signs and symptoms of rheumatoid arthritis and osteoarthritis. ORUDIS is indicated for the management of pain and for the treatment of primary dysmenorrhea
Dosage Form(s):	25 mg, 50 mg and 75 mg capsules 100 mg, 150 mg and 200 mg extended-release capsules
Route of Administration:	Oral
Related Reviews:	NSAIDs class labeling guideline
Submitted:	The sponsor requested labeling revisions as follows:

A. Under "ADVERSE REACTIONS section, INCIDENCE LESS THAN 1% (PROBABLE CAUSAL RELATIONSHIP)"

1. Added a new subsection "Digestive" and included "hepatitis, cholestatic hepatitis" as additional adverse event terms.

2. Relocated the term "hepatic dysfunction" from the "Metabolic and Nutritional" subsection to the "Digestive"

subsection.

3. Added "toxic epidermal necrolysis, erythema multiforma, Stevens-Johnson syndrome" adverse event terms to the "Skin and Appendages" subsection.

The submission of MedWatch forms and published articles supported the additions of all the above mentioned adverse events. (1 case for TEN with article, 2 cases for erythema multiforma, 2 cases for Stevens-Johnson Syndrome with foreign articles, 5 cases for hepatitis and 4 cases for cholestatic hepatitis with articles)

B. Revised (text in bold) the last sentence of paragraph four to read as: "Rare adverse reactions (incidence less than 1%) were collected form **one or more of the following sources:** foreign reports to manufacturers and regulatory agencies, publications, U.S. Clinical trials, **and/or U.S. postmarketing spontaneous reports**."

Recommendation:

The proposed changes, except cholestatic hepatitis, would be required to be all NSAIDs labeling once this Class labeling has been finalized. Thus, we have no objection if the sponsor wishes to include in their labeling at this time.

An **APPROVAL** letter should be sent to the sponsor.

Marina Y. Chang, R. Ph.

Christina Fang, M.D.

cc: orig NDA 18-754
HFD-550
HFD-550/MO/Fang
HFD-550/SMO/Hyde
HFD-550/Act Div Dir/Chambers MAC 2/20/97
HFD-550/SChem/Patel
HFD-550/SPharm/Chen
HFD-550/Clin/Chang
HFD-550/CSO/LoBianco
NDA 19-816

ORIGINAL

WYETH-AYERST ® *RESEARCH*

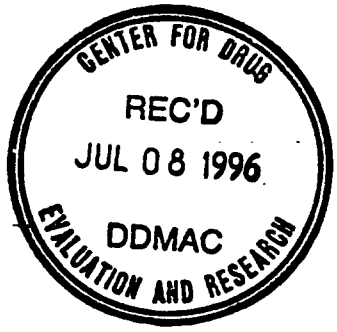
P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

ORIGINAL

July 3, 1996

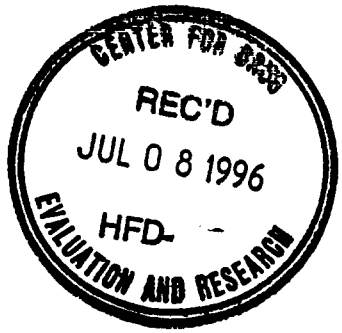


Oruvail® Extended-Release Capsules
NDA No. 19-816

NDA NO. 19816 REF. NO. S-007

NDA SUPPL FOR Draft

Wiley Chambers, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Document Control Room, 9B-23
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706



Labeling Supplement

Dear Dr. Chambers:

Reference is made to our approved New Drug Application No. 19-816 for Oruvail, ketoprofen, Extended-Release Capsules.

The purpose of this submission is to supplement the Oruvail NDA to provide for the following changes in the text of the physician's package insert common to both Oruvail and Orudis® Capsules.

The enclosed draft labeling has been revised to incorporate additional adverse event terms resulting from domestic and international postmarketing reports received at Wyeth-Ayerst. We propose the following changes in the "Adverse Reactions" section of the insert.

1. "INCIDENCE LESS THAN 1% (PROBABLE CAUSAL RELATIONSHIP)" subsection.

A. "Digestive:" heading

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS 1-10-97 DATE

The following additional adverse event terms will be included at the end of the existing text under this heading.

" hepatitis, cholestatic hepatitis"

Also, the term **"hepatic dysfunction"** will be deleted from the **"Metabolic and Nutritional:"** heading and added to the **"Digestive:"** heading with the terms listed above. The term **"jaundice"** will be similarly relocated to this heading from the **"Digestive"**events in the "INCIDENCE LESS THAN 1% (CAUSAL RELATIONSHIP UNKNOWN)" subsection. The end of the text will therefore read as follows.

", hepatic dysfunction, hepatitis, cholestatic hepatitis, jaundice."

B. "Skin and Appendages:" heading

The following additional terms will be included at the end of the existing text under this heading.

"toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome."

2. The last sentence of paragraph four of the "Adverse Reactions" section currently reads as follows:

> "Rare adverse reactions (incidence less than 1%) were collected from foreign reports to manufacturers and regulatory agencies, publications, and U.S. clinical trials."

Due to the fact that some of the ADE reports responsible for the proposed text changes were from domestic sources, we have revised the aforementioned statement to read as follows. (Please note that the revised text has been bolded to facilitate review; it will not appear as bolded in the final printed labeling).

> "Rare adverse reactions (incidence less than 1%) were collected from **one or more of the following sources:** foreign reports to manufacturers and regulatory agencies, publications, U.S. clinical trials**, and/or U.S. postmarketing spontaneous reports.**"

Attachment 1 is a draft copy of the amended Oruvail®/Orudis® package insert, with annotations describing the additions, deletions and revisions to the current direction circular.

Attachment 2 provides photocopies of the adverse event reports received at Wyeth-Ayerst that formed the basis of our decision to revise the package insert.

We are simultaneously submitting a supplement to the Orudis Capsule New Drug Application (NDA No. 18-754) to provide for the labeling changes described in this letter.

We trust that you will find the enclosed proposed labeling satisfactory, and will so advise us at your earliest convenience. Should you have any questions regarding this submission, please telephone the undersigned at (610) 902-3761, or Mr. John Seneca at (610) 902-3724.

Sincerely,

WYETH-AYERST LABORATORIES

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

JOS/JS:ag

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JUL 15 1996

NDA No. 19-816

James O'Shaughnessy
Wyeth-Ayerst Laboratories
170 Radnor Chester Road
St. Davids, PA 19087-4288

Attention: James O'Shaughnessy

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Oruvail Extended-Release Capsules

NDA Number: 19-816

Supplement Number: S-007

Date of Supplement: July 3, 1996

Date of Receipt: July 8, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 6, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic & Dental Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-550
Rockville, MD 20857

Sincerely yours,

Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research