NDA 20-584
S-001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-584/S-001

FEB - 3 1998

Wyeth-Ayerst Laboratories
Attention: James J. O'Shaughnessy
Associate Director, U.S. Regulatory Affairs
170 Radnor-Chester Road
St. Davids, PA 19087-5221

Dear Mr. O'Shaughnessy:

Please refer to your November 27, 1996, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lodine XL (etodolac extended-release tablets) 400 mg and 600 mg. In addition, also refer to our May 29, 1997, approvable letter for SLR-001.

We acknowledge receipt of your submission dated July 22, 1997, and January 20, 1998.

The supplemental application provides for changes in the Description and How Supplied sections of the package insert for the addition of the 500 mg tablet, approved January 20, 1998.

We have completed the review of this supplemental application, including the submitted draft labeling, 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 draft labeling submitted on January 20, 1998. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on January 20, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

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 "FINAL PRINTED LABELING" for approved NDA 20-584. Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required. Additionally, we remind you of our request to conform to the NSAID class labeling template of December 20, 1996.

If you have any questions, please contact D'Annie Gunter, P.D., Project Manager, (301) 827-2090.

Sincerely,

JEH 2-3-98

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

cc:
NDA 20-584
Div. files
HF-2/Med Watch (with draft labeling)
HFD-613/OGD (with draft labeling)
HFD-40/ DDMAC (with draft labeling)
HFA-100
HFD-830/Chen
DISTRICT OFFICE
HFD-80
HFD-550/Gunter
HFD-550/Koerner
HFD-550/Yaciw/Patel

saved as n: 20584s1a.wpd

APPROVAL (AP)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA

DRAFT LABELING IS **NO LONGER** BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

12 pages

FEB 3 1998

NDA 20-584/S-001

Labeling Review

NDA:	20-584/S-001
Applicant:	Wyeth-Ayerst Research
Applicant Representative:	Vern DeVries, Ph.D.
Drug:	Lodine XL (etodolac extended-release tablets) 500mg
Submission Date:	November 27, 1996
Related Submissions:	July 22, 1997 and January 20, 1998
Review Date:	January 23, 1998
Project Manager:	Gunter

Overview:
This supplement provides for changes in the Description and How Supplied sections of the package insert for the addition of a 500mg tablet S-002, which was approved January 23, 1998.

Review:
Approval. Sponsor submitted a change in dosage strength, 500mg tablet, in addition to the already approved 400mg and 600mg tablets. Only the changes specified in the Description and How Supplied Sections of the Lodine XL (etodolac extended-release tablets) Package Insert reflecting the inclusion of the 500mg tablets are approved. The language in the remaining sections of the labeling are identical to the previously approved labeling of October 2, 1996.

Recommendation:

The Sponsor should be issued an approval letter.

2-3-98

Reviewer
D'Annie Gunter, P.D.

Medical Officer
John Hyde, Ph.D., M.D.

cc:
NDA 20-584
Divisional Files
HFD-550/Gunter/Koerner/Hyde

D IV

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-584/S-002

JAN 23 1998

Wyeth-Ayerst Laboratories
Attention: James J. O'Shaughnessy
Associate Director, U.S. Regulatory Affairs
170 Radnor-Chester Road
St. Davids, PA 19087

Dear Mr. O'Shaughnessy:

Please refer to your November 27, 1996, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lodine XL (etodolac extended release tablets), 400 mg and 600 mg. Please also refer to our letter of May 29, 1997.

We acknowledge receipt of your submission dated July 22, 1997.

The supplemental application provides for the addition of a 500 mg tablet.

We have completed the review of this supplemental application and it is approved.

Please be advised that this approval affects only those changes specifically submitted in this supplemental new drug application. 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.

If you have any questions, please contact Chin Koerner, Project Manager, (301) 827-2090.

Sincerely,

JEH 1-23-98

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

CC:
NDA 20-584
Div. files
HFA-100
HFD-830/Chen
DISTRICT OFFICE
HFD-80
HFD-550/C.Koerner
HFD-550/Yaciw/Patel

saved as S-0038.120

APPROVAL (AP)

Etodolac Extended Release Tablets
400, 500, and 600mg tablets
NDA 20-584 SCF-002/SLR-001
Lodine® XL
Reviewer: E.D. Bashaw, Pharm.D.
APW

Wyeth-Ayerst Research
Philadelphia, Pa 19101

Submission Date:
07/22/97

Review of Responses

Background

Lodine® XL was originally approved as a 400 and 600mg controlled release tablet. To provide for maximum flexibility the sponsor decided to develop a 500mg XL companion product. This range of strengths would fill in the current 400mg gap between the 800mg dose (2x400mg) and a 1200mg dose (2x600mg). These responses were sent in originally in late 1996 as responses to labeling (SLR-001 and -002). In mid-1997 it was decided that this classification was incorrect and the document was split into a chemistry supplement (SCF-002) and a revised labeling supplement (SLR-001). In the list of items the sponsor has responded to there was one biopharmaceutic issue that has been referred to the Division of Pharmaceutical Evaluation for consideration.

Comment #7

It is not clear why the bioequivalence study compared an 800mg dose to a 1000mg dose. Please provide an explanation of why the bioequivalence study compared an 800mg dose to a 1000mg dose instead of comparing 1000mg to 1000mg.

Sponsor's Response

Lodine® XL is commercially available as a 400mg tablet or a 600mg tablet. It was the sponsor's decision that rather than trying to split the 600mg tablet or to give 1 of each (400 and 600mg) tablet that a scaling approach of 2x400mg was more reasonable. The sponsor also cited that this approach was also used in the approval of the 500mg IR tablet and they were under the impression that the approach was acceptable to the FDA.

FDA Response

In the original comment the reviewer was referring to a direct comparison of the 500mg IR tablet to the 500mg XL tablet at the 1000mg dosage level. The reviewer never intended for the sponsor to attempt to split or combine dosage strengths to make the 1000mg dose. The approach that was chosen by the sponsor is an acceptable one, but a direct comparison of the IR to XL dosage form would have been a relevant and useful comparison.

Recommendation

While the sponsor did not directly address the issue raised in comment #7, the information they provided does provide an adequate rationale for closure to this issue. No further action is indicated in relation to this issue.

E. Dennis Bashaw, Pharm.D. 1/4/97
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

Secondary Review, John Lazor, Pharm.D 1/20/98
TL, Antivirals

CC: NDA 20-584 (ORIG),
HFD-550/DIV File
HFD-550/CSO/Koerner
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy
HFD-344(Viswanathan)

JAN 9 1998

Chemistry Review #2	1. Division HFD-550	2. NDA Number 20-584
3. Name and Address of Applicant Wyeth-Ayerst Laboratories 170 Radnor-Chester Road St. Davids, PA 19087-5292	4. Supplement Number Date Stamp Date Due Date SCF-002 [11/27/96 11/29/96 5/29/97] SLR-001 [11/27/96 11/29/96]	
5. Name of Drug Lodine® XL	6. Nonproprietary Name etodolac	
7. Supplement Provides for: addition of a 500 mg tablet		8. Amendment(s) AZ 7/22/97 rec'd 7/23/97 due 1/23/98
9. Pharmacological Category NSAID	10. How Dispensed R	11. Related Documents
12. Dosage Form extended release tablet	13. Potency(ies) 400 and 600 mg tablets plus proposed 500 mg	
14. Chemical Name and Structure see USAN		
15. Comments This submission was administratively split into SCF-002 and SLR-001. An APPROVABLE letter was issued 5/29/97. This amendment is a response to that letter. The Description and How Supplied sections of the package insert submitted as attachment 6 of the 7/22/97 amendment are acceptable.		
16. Conclusions and Recommendations Supplements may be APPROVED from the CMC standpoint.		
17. Name Charlotte A. Yaciw	Signature	Date 1/9/98
Concurrence		1-9-98

cc:

NDA 20-584/S001 & S002
HFD-550/Division File
HFD-550/Chem/Yaciw
HFD-550/CSO/Koerner
HFD-830/DD/Chen

Doc ID: n20584s2.001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-584/S-001
NDA 20-584/S-002

MAY 29 1997

Wyeth-Ayerst Laboratories
Attention: James J. O'Shaughnessy
Associate Director, U. S. Regulatory Affairs
170 Radnor-Chester Rd.
St. Davids, PA 19087-5292

Dear Mr. O'Shaughnessy:

Please refer to your November 27, 1996, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lodine (R) XL (etodolac extended-release tablets).

These supplemental applications provide for the introduction of a 500 mg Lodine XL Tablet and the associated labeling changes.

We have completed the review of these supplemental applications, and they are approvable. Before these applications may be approved, however, it will be necessary for you to satisfactorily address the following deficiencies:

1. A complete list of the container/closure presentations to be used for the 500 mg tablet including the number of tablets per container has not been provided. This information should be provided. Please also indicate clearly those presentations which are intended for marketing, physician samples, or other uses.

2. Complete data on the container/closure components for all presentations including information pertaining to resin used and physical and chemical characteristics has not been provided. This information should be provided. Please also provide any test results which support suitability for the drug product. If any of the information is identical to the 400 and 600 mg tablet submission, please state it as such.

3. The procedure used to collect the stability data is not clear. Please submit the stability protocol used to generate the data submitted. If a matrix approach is used, please provide the matrix table.

4. The container/closure presentations which are to be included in the post approval stability protocol are not clearly identified. Please submit a revised protocol to be used for the post approval stability studies.

5. Chemistry/Manufacturing Controls information for the 500 mg tablets does not contain specific data on bottles of 30 tablets. For stability purposes, if bracketing is used, it should only include commercial size bottles. Stability data for any sample packages should be submitted in addition.

6. The submitted draft labeling is not consistent with the NSAID class labeling template of December 20, 1996. Please submit revised draft labeling which is consistent with the NSAID class labeling template.

7. It is not clear why the bioequivalence study compared an 800 mg dose to a 1000 mg dose. Please provide an explanation of why the bioequivalence study compared an 800 mg dose to a 1000 mg dose instead of comparing 1000mg to 1000mg.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the supplemental applications. 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.

If you have any questions, please contact Chin Koerner, Project Manager, (301) 827-2090.

Sincerely,

WAC 5/29/97

Wiley A. Chambers, M.D.
Acting Division Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:

NDA 20-584
HFD-550/Div. Files
HFD-550/CSO/Koerner
HFD-550/Yaciw, Patel
HFD-830/Chen
HFD-92
DISTRICT OFFICE
HFD-232
HFD-105
HFD-550/SPMS/LoBianco
HFD-550/MO/Hyde

APPROVABLE (AE)

MAY 27 1997

Chemistry Review	1. Division HFD-550	2. NDA Number 20-584
3. Name and Address of Applicant Wyeth-Ayerst Laboratories 170 Radnor-Chester Road St. Davids. PA 19087-5292	4. Supplement Number Date Stamp Date Due Date SCF-001 11/27/96 11/29/96 5/29/97 SLR-002 11/27/96 11/29/96	
5. Name of Drug Lodine® XL	6. Nonproprietary Name etodolac	
7. Supplement Provides for: addition of a 500 mg tablet		8. Amendment(s)
9. Pharmacological Category NSAID	10. How Dispensed ℞	11. Related Documents
12. Dosage Form extended release tablet	13. Potency(ies) 400 and 600 mg tablets plus proposed 500 mg	
14. Chemical Name and Structure see USAN		

15. Comments

This submission was administratively split into SCF-001 and SLR-002.

Page 012 of volume states that the proposed 500 mg tablet is a proportionate of the 600 mg Wyeth has submitted the CMC information for the 500 mg tablet.

Compliance clearance was requested 3/10/97. It has not yet been completed.

Labeling is in volume 7.

16. Conclusions and Recommendations
Supplement is APPROVABLE.

17. Name	Signature	Date
Charlotte A. Yaciw		5/22/97
Concurrence		5/22/97

cc:

NDA 20-584/S001
HFD-550/Division File
HFD-550/CYaciw
HFD-550/CSO/Koerner

Acceptable EER issued 5/27/97.
Copy attached. CY 5/27/97

Doc ID: n20584s.001

APR - 9 1997

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 20-584 (SLR-001) **SUBMISSION DATE:** 11/27/96
PRODUCT: Etodolac Extended-Release Tablets, 500 mg
BRAND NAME: LODINE® XL
SPONSOR: Wyeth-Ayerst Laboratories **REVIEWER:** Dan Wang, Ph.D.
170 Radnor-Chester Rd.
St. Davids, PA 19087-5292 **TYPE OF SUBMISSION:** Supplement

BACKGROUND

This NDA supplement is referencing the applicant's recently approved NDA 20-584 for Lodine® XL (etodolac extended-release tablets), 400 mg and 600 mg. As in the case of the existing Lodine XL dosage strengths, the 500 mg tablet will be indicated for management of the signs and symptoms of osteoarthritis and rheumatoid arthritis. The applicant indicated that the purpose of this supplement application is to provide for the introduction of a 500 mg Lodine XL Tablet. The approved dosing range for Lodine XL Tablets is 400 mg to 1000 mg per day.

In addition to chemistry, manufacturing and controls information, a bioavailability study was also included in this submission. This study was designed to demonstrate the relative bioavailability of the new 500 mg etodolac extended-release tablet formulation to 400 mg tablet under fed and fast conditions after multiple dose administration. Dissolution results for 400mg and 500 mg tablets, and dissolution specification criteria for 500 mg tablet were also submitted.

SUMMARY OF THE STUDIES

1. BIOAVAILABILITY STUDY

TITLE: The comparative bioavailability of multiple doses of Etodolac ER in healthy subjects receiving a newly formulated 500 mg tablet versus a 400 mg tablet under both fed and fasting conditions (Protocol 0654C-133-US)

INVESTIGATOR:

STUDY CENTER:

STUDY PERIOD: Date of first enrollment: Nov. 29, 1995. Date of last completion: Dec. 12, 1995

OBJECTIVES: 1) To compare the bioavailability of two etodolac extended-release oral tablet formulations: 500 mg tablets and previously existing 400 mg tablets. 2) To evaluate food effect on both formulations.

FORMULATIONS: A. Etodolac ER 400 mg tablet. Batch number: 3WCZ. Batch size: Control number: 9510755. Formulation number: 0929524C. B. Etodolac ER 500 mg tablet. Batch number: A95D048. Batch size: Control number: 9510754. Formulation number: 0930528C. For detailed formulation information, see attached Table 1.

STUDY DESIGN: This is a multiple-dose, open-label, randomized, crossover design study. Twenty eight healthy subjects (16 males and 12 females, age ranged from 20 to 41 years old) were enrolled on this study. Demographic information is shown in Table 6. One woman (subject 15) and three men (subjects 16, 21, 22) were included in the study but had body weights that exceeded their ideal weight by more than 15%, with the largest deviation of 22% (subject 22).

Subjects received in a randomized order either 2x400 mg etodolac ER or 2x500 mg etodolac ER for 7 days each treatment (days 1-7 and days 8-14). Throughout the study, at approximately 8 am each day, subjects received an oral dose of etodolac ER with 240 ml of water. No additional water was allowed until 2 hours after the dose. A light breakfast (except on study days 6, 7, 13, and 14) that contained not more than 400 calories and 12 g of fat was provided approximately 2 hours after the dose. The dining schedule was as follows: a light breakfast at 10 am, lunch at noon, dinner at 5 pm, and a snack at 9 pm. Subjects began a 10 hour overnight fast at 10 pm each night. On days 6 and 13, after the morning dose, subjects fasted for an additional 4 hours after dose. On study days 7 and 14, subjects were served a high-fat breakfast 30 minutes before dose administration. The meal met FDA specifications for a high-fat breakfast and consisted of 2 large eggs, 2 strips of bacon, 2 pieces of toast with butter, 4 ounces of hashed browned potatoes, and 8 ounces of whole milk. The subjects were to steadily consume the meal over 20 minutes.

On days 6, 7, 13 and 14, serial blood samples were collected before (0 hour) and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after dose administration. Additional blood samples were collected after the dose on day 14 at the 30 and 36 hour time points.

ASSAY:

DATA ANALYSIS:

1) Pharmacokinetic analysis: Noncompartmental method was used to calculate Cmax, AUC, $t_{1/2}$, CL/F, V/F, etc. The AUC values were determined by using the trapezoidal rule during the ascending portion of the curve and the log-trapezoidal rule during the descending portion of the curve. For CL/F and V/F, the parameters were normalized to the individual subject's body weight. For calculation of the (S)-etodolac parameters for CL/F and V/F, one half of the administered racemate dose was assumed to account for (S)-enantiomer component. The fraction of dose absorbed versus time was determined using the Wagner-Nelson method as described in the following equation:

$$\frac{(X_a)_T}{(X_a)_\infty} = \frac{C_T + \lambda_z AUC_T}{\lambda_z AUC}$$

2) Statistical analysis: For racemic etodolac, the concentrations of etodolac in plasma and the dose dependent pharmacokinetic parameters determined on days 6, 7, 13, and 14 were normalized to the 2x400 mg dose and then compared by using ANOVA that included the effects of sequence, subject nested within sequence, period and treatment. The pharmacokinetic parameters were also compared between fasting and fed conditions by using ANOVA that included the effects of subject and treatment.

For (S)-etodolac, the concentrations in plasma and the pharmacokinetic parameters determined on days 6 and 13 were compared by using ANOVA that included the effects of sequence, subject nested within sequence, period, and treatment.

RESULT: One subject (subject 26) dropped out of the study after enrollment but before receiving a dose. All subjects expect subject 26 were included in the pharmacokinetic analysis.

1. Racemic etodolac

The individual concentrations of racemic etodolac under fasting and fed conditions are shown in Table 7A. The mean (SE) of racemic etodolac concentrations versus time under both the fasting and fed conditions are shown in Figure 1A. Individual pharmacokinetic parameters for the 400 mg and 500 mg formulations under both the fasting and fed conditions are presented in Table 8A. The mean values (CV%) for AUC, Cmax and Tmax are shown in the following table:

	AUC_{0-24} (mg.h/L)	Cmax (mg/L)	Cmin,before dose (mg/L)	Cmin,after dose (mg/L)	Tmax (h)
2x400 mg (fasted)	300 (64)	21.7 (51)	6.38 (99)	6.09 (103)	4.9 (48)
2x400 mg (fed)	345 (55)	36.1 (33)	8.59 (93)	5.15 (106)	6.0 (28)
2x500 mg (fasted)	391 (57)	28.4 (50)	7.65 (113)	7.35 (111)	4.7 (55)
2x500 mg (fed)	430 (51)	50.0 (35)	9.95 (78)	6.99 (111)	5.3 (34)

The variability of AUC and Cmax values ranges from 33 to 64%. When comparing treatments under the fasted and fed treatments, the variability of the fasted treatment group is about 6 to 20% higher. There seems to be no difference in variability between the 2x400 mg treatment group and 2x500 mg treatment group under both fasted and fed conditions.

It is also observed that food increased Cmax by 66% and 76% for 2x400 mg and 2x500 mg, respectively. Food delayed the Tmax by approximately 1 hour. However, the extent of absorption is not dramatically affected by food in terms of AUC (increase of 15% and 10% for 2x400 mg and 2x500 mg, respectively).

It is of the reviewer's interest to mention that the magnitude of increase in AUC and Cmax values may be a little less than it appears to be in the above table and also in Figure 1A. This is because that the predose concentration of fasted treatment is lower than that of fed treatment. This difference is a result of food effect. The result of the food effect study shows that food significantly increased Cmax but decreased Cmin. On day 5 and day 12, each subject had a breakfast 2 hours after the dose. On day 6 and day 13, subjects fasted for 4 hours after the dose. Although not to a large extent, the breakfast on days 5 and 12 may influence the absorption of the drug, which is a extended-release product, so that the predose levels on days 6 and 13 are lower than those on days 7 and 14. The high predose concentration of the fed treatment may lead to an over estimation of increase in Cmax under fed condition. However, for this study, this over estimation does not significantly affect the outcome of the study.

Statistical analysis results are shown in Tables 10A and 11. The geometric mean values of the important PK parameters that reflect bioavailability and statistical analysis results are also summarized below:

	AUC_{0-24}*(mg.h/L)	Cmax*(mg/L)	Tmax(h)
2x400 mg (fasted)	271	19.7	4.47
2x500 mg (fasted)	287	20.8	4.22
Ratio(2x500/2x400, fasted)	106	106	95
90% CI (%)	98-115	96-117	83-108
2x400 mg (fed)	318	34.6	5.75
2x500 mg (fed)	320	38.0	5.02
Ratio(2x500/2x400, fed)	101	110	87
90% CI (%)	97-105	104-117	78-98

*AUC and Cmax values are normalized to 2x400 mg dose

Comparison of the dose-normalized Cmax and AUC values for 400 mg and 500 mg formulations revealed that bioequivalence criteria were met under both the fasting and fed conditions. Although there is significant difference between dose normalized Cmax values under the fed condition, they are still considered bioequivalent since the 90% confidence interval falls within the range of 80 to 125%.

2. (S)-Etodolac

(S)-etodolac was measured only for the treatment under fasted condition. The mean plasma concentrations and PK parameters are shown in Tables 9B and 10B. The mean plasma concentrations for (S)-etodolac and racemic etodolac are also shown in Figure 1B. Mean values for AUC and Cmax are summarized below:

	AUC_{0-t} (mg.h/L)	Cmax (mg/L)
2x400 mg (fasted)	21.98 (38)	2.21 (47)
2x500 mg (fasted)	24.92 (37)	2.42 (43)

Treatment-related difference between dose groups were observed. Dose-normalized AUC is 12% higher for the 500 mg formulation that the respective 400 mg formulation.

In Figure 10, the results of a Wagner-Nelson analysis based on the mean concentrations of total- and (S)-etodolac are depicted. The mean profiles show little difference in the rate of absorption between the racemate and the (S)-enantiomer, with most or all of the available drug absorbed within 12 hours after the dose. It is also observed that there was a delay in absorption when food was given at 4 hours after the dose.

CONCLUSION:

Under either the fasting or fed condition, the 400-mg and 500-mg strength tablets of etodolac ER are bioequivalent, when the data are normalized for dosage strength. Data for the comparisons of the fasting and fed conditions are consistent with previous data indicating that food does not significantly affect the extent of absorption but does increase the peak concentration by approximately 60 to 70% for both 2x400 mg and 2x500 mg treatments.

2. DISSOLUTION

1. Summary of Methods and Results

A summary of the dissolution profiles of the etodolac ER 400- and 500-mg tablets are shown in Table D.1; proposed product dissolution specifications are shown in Table D.2.

TABLE D.1: ETODOLAC ER DISSOLUTION PROFILES

Date of Test	Dosage Form and Strength	Batch Number [Formulation]	Time (hours)	% Released (range) [a]	% Released (mean) [a]	%Coefficient of Variation
November 1995	Etodolac ER 400 mg tablets	3WCZ [0929524C]	2		22	3.7
			4		39	6.3
			8		69	6.7
			14		95	4.3
November 1995	Etodolac ER 500 mg tablets	A95D048 [0930528C]	2		22	5.0
			4		40	5.1
			8		72	4.6
			14		98	1.0

[a] Data derived from mean of 12 observations per time point.

COMMENT

1. The effect of food on the absorption of extended-release formulation could be still significant when food is taken 2 hours after the dose. Therefore, the predose level for the next dose may be different from that when the previous dose is taken under fasted condition. This should be taken into consideration should the applicant design a future crossover food effect study under steady-state condition or after multiple dose administration of the study drug.

RECOMMENDATION

The applicant has adequately conducted the bioavailability study submitted in this NDA supplement. The study results indicate that when normalized for dose, the 500 mg oral tablet was shown to be bioequivalent to the 400 mg oral tablet formulation in terms of racemic etodolac bioavailability. The dissolution method and specification criteria are acceptable to the Agency. The applicant should be informed of COMMENT #1.

4/9/97

Dan Wang
Division of Pharmaceutical Evaluation III

FT initialed by D. Bashaw, Pharm.D. 4/9/97

cc:
NDA 20-584(Original)
HFD-550(Koerner)
HFD-880(N. Fleischer)
HFD-880(Bashaw)
HFD-880(Wang)
~~HFD-850(Mira Millison; Drug; Chron Files)~~
HFD-205(FOI)
HFD-344(Viswanathan)
CDR: Attn: Barbara Murphy

TABLE 1. ETODOLAC ER TEST FORMULATIONS

Ingredients [a]	Formulation 0929524C Etodolac ER Tablet 400 mg	Formulation 0930528C Etodolac ER Tablet 500 mg
Active		
Etodolac, Micronized	400 mg	500 mg
Inactive		
Ethylcellulose, NF, 7cps		
Hydroxypropyl Methylcellulose, 2208, USP, 100 cps		
Lactose, NF, Monohydrate		
Dibasic Sodium Phosphate, USP		
Magnesium Stearate, NF		
Coating Ingredients:[c]		

a mg per tablet.
b Removed during processing.
c Approximate amount per tablet depending on pan size, lot size, etc.

ORIGINAL

NDA NO. 20584 REF. NO. 5

NDA SUPPL FOR Labeling

WYETH-AYERST RESEARCH

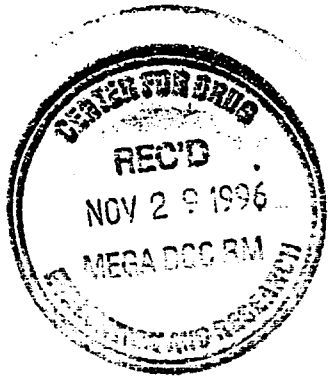
P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

November 27, 1996

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



REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Wiley Chambers, 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
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Chambers:

Supplemental Application

Reference is made to our recently approved New Drug Application No. 20-584 for Lodine® XL (etodolac extended-release tablets), 400 mg and 600 mg. As in the case of the existing Lodine XL dosage strengths, the 500 mg tablet will be indicated for management of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

The purpose of this supplemental application is to provide for the introduction of a 500 mg Lodine XL Tablet. The approved dosing range for Lodine XL Tablets is 400 mg to 1000 mg per day.

In support of this submission we have enclosed chemistry, manufacturing and controls information, as well as data to demonstrate the relative bioavailability study comparing multiple doses of the new 500 mg etodolac extended-release tablet formulation to one 400 mg tablet under fed and fast conditions.

No clinical data. Chem & Biopharm
No data review by chem & Biopharm
John Hyde 12-10-96

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TH-1330

Wyeth-Ayerst hereby certifies that a field copy of the Chemistry, Manufacturing and Controls section, application form and application summary of this supplemental application have been forwarded to the Philadelphia District Office, the FDA home office for Wyeth-Ayerst Laboratories, as required under 21 CFR 314.50 (d)(1)(v).

We trust that you will find the enclosed information satisfactory and that this supplemental application will be approved at your earliest convenience. Should you have any questions regarding this submission, please contact the undersigned at (610) 902-3761 or Mr. John Seneca at (610) 902-3724.

Sincerely,

WYETH-AYERST LABORATORIES

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

JOS:ag

Attachments

ORIGINAL

WYETH-AYERST RESEARCH

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

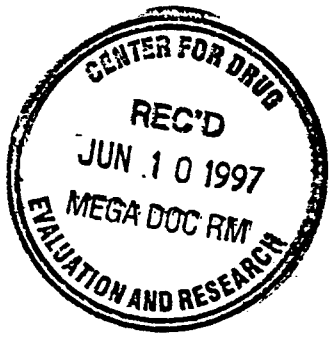
Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

June 9, 1997

NDA No. 20-584/S-001
NDA No. 20-584/S-002
Lodine® XL

SUPPL NEW CORRESP



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
9201 Corporate Blvd.
Rockville, MD 20850

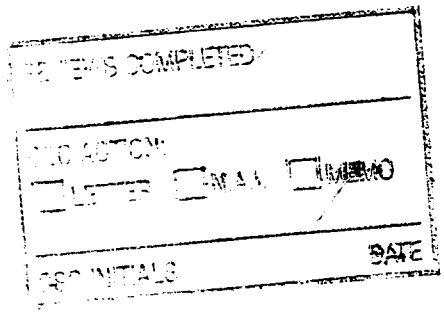
Dear Dr. Chambers:

Reference is made to our approved New Drug Application No. 20-584 for Lodine® XL, etodolac extended-release tablets, and to our November 27, 1996 supplemental New Drug Applications S-001 and S-002, providing for the introduction of a 500 mg tablet and the associated labeling changes. Reference is also made to the May 29, 1997 letter from the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP), received by fax at Wyeth-Ayerst on June 5, 1997, advising that S-001 and S-002 are "approvable."

The purpose of this letter is to advise you that as per the provisions of 21 CFR 314.110(a)(1), we intend to exercise our option to amend Lodine® XL supplemental applications S-001and S-002.

Sincerely,

WYETH-AYERST LABORATORIES



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

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Voted
J Hyde 6-13-97
Voted Ja 6/16/97