

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**018922Orig1s005**

***Trade Name:*** LODINE

***Generic or  
Proper Name:*** etodolac

***Sponsor:*** Wyeth-Ayerst Laboratories

***Approval Date:*** 01/12/1993

***Indication:*** LODINE is indicated for acute and long term use in the management of signs and symptoms of osteoarthritis. Lodine is also indicated for the management of pain.

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:  
NDA 018922/S-005**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 018922/S-005**

**APPROVAL LETTER**

NDA 18-922/S005

JAN 12 1993

Wyeth-Ayerst Laboratories  
P. O. Box 8299  
Philadelphia, Pennsylvania 19101-1245

Attention: James J. O'Shaughnessy  
Manager  
Drug Regulatory Affairs

Dear Mr. O'Shaughnessy:

Please refer to your July 17, 1992 supplemental new drug application for Lodine (etodolac) capsules submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act.

The supplement requests an additional control for the drug substance and provides revised specifications and a new thin-layer chromatography (TLC) method. We have completed the review of this application and it is approved as of the date of this letter.

To complete our records, please submit the Rf's for compounds as indicated in the typical chromatogram submitted in Figure 2, page 24 of the supplement.

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

Should you have any questions, please contact Mrs. Mary L. Owens, Project Manager, 301-443-3741.

Sincerely yours,

Ernest G. Pappas  
Review Chemist  
Pilot Drug Evaluation Staff, HFD-007  
Center for Drug Evaluation and Research

cc:

NDA 18-922/S005

HFD-007/DivFile

HFD-007/MLOWens12-17-92

HFC-130/JAllen

HFD-007/EGPappas

HFD-102

HFD-340

R/D init by: Fran LeSane 12/17/92

Charlotte Yaciw 12/7/92

1/11/93 mlo

egg 1/11/93 coy

1-12-93

FT by: J.Veach 12/31/92

supap.LOD

SUPPLEMENT APPROVAL

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 018922/S-005**

**CHEMISTRY REVIEW(S)**

**NDA SUPPLEMENT REVIEW**

DEC 7 1992

<b>CHEMIST'S REVIEW</b>	<b>1. ORGANIZATION</b> PDES (HFD-007)	<b>2. NDA NUMBER</b> 18-922
<b>NAME &amp; ADDRESS OF APPLICANT</b> Wyeth-Ayerst Laboratories, Inc. P.O. Box 8299 Philadelphia, Pa. 19101-1245		<b>4. AF NUMBER</b>
		<b>5. SUPPLEMENT(s) NUMBER(s) DATE(s)</b>
<b>6. NAME OF DRUG</b> Lodine	<b>7. NONPROPRIETARY NAME</b> etodolac	<b>S-005 7/17/92</b>

<b>8. SUPPLEMENT(s) PROVIDES FOR:</b>  <b>S-005</b> Provides for a new thin-layer chromatography (TLC) method to quantitatively determine [redacted] (b)(4), a potential impurity in etodolac drug substance. The supplement also provides for revised specifications to reflect limits of not more than [redacted] (b)(4) of the [redacted] (b)(4) in the etodolac drug substance.	<b>9. AMENDMENTS AND OTHER (REPORTS, etc.) DATES</b> none
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<b>10. PHARMACOLOGICAL</b> Anti-inflammatory Agent	<b>11. HOW DISPENSED</b> XXX x Rx OTC	<b>12. RELATED IND/NDA/DMF(s)</b>
<b>13. DOSAGE FORM(s)</b> Tablets	<b>14. POTENCY(ies)</b> 100 mg, 200 mg & 300 mg	

<b>15. CHEMICAL NAME AND STRUCTURE</b>  m.w. . CAS Registry No. - -	<b>16. RECORDS AND REPORTS</b> CURRENT x Yes No REVIEWED x Yes No
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**17. COMMENTS**

The firm proposed a new TLC method to quantitatively determine [redacted] (b)(4), a potential impurity which may arise from the synthesis of etodolac drug substance and revised specifications for the etodolac drug substance to limit the [redacted] (b)(4) to NMT [redacted] (b)(4). This change gives added assurance of identity, strength, quality and purity for etodolac drug substance. In support of this change, the following information was submitted:

- \* The structural formula for etodolac and [redacted] (b)(4)
- \* Revised specifications and tests for the NDS.
- \* Analytical Method No. [redacted] (b)(4) for determining [redacted] (b)(4) in etodolac NDS by TLC.
- \* Suitability study for the use of Method No. [redacted] (b)(4).
- \* Summaries and abstracts of toxicology studies using etodolac drug substance (AY-24,236) containing [redacted] (b)(4) of [redacted] (b)(4) previously submitted to the Agency noted (see firm's letter, page 2).

(see page 3 of chemist review for details)

**18. CONCLUSIONS AND RECOMMENDATIONS**

The minor changes proposed in the supplement are improvements in the analytical controls. They give added assurance of identity, strength, purity and quality of for etodolac active material. Recommend approval letter to issue for the supplement. CSO should draft approval letter.

CSO should request the Rf's for compounds as indicated in the typical chromatogram submitted in Figure 2, page 15 of the supplement. This information should not hold up the approval of the supplement; it only makes the records complete.

CSO should refer toxicology studies, as indicated on page 2 of the supplement, to our pharmacologists for concurrence to approve this supplement.

19.		REVIEWER	
NAME	SIGNATURE	DATE COMPLETED	DATE COMPLETED
Ernest G. Pappas	<i>Ernest G. Pappas</i>	12/4/92	12/4/92
DISTRIBUTION	ORIGINAL JACKET	REVIEWER	DIVISION FILE

*again, please*  
12-7-92

**Chemist Review Notes**

\* The structural formula for etodolac and [REDACTED] (b) (4)

IODINE CAPSULES  
200 mg, 300 mg



ETODOLAC



(b) (4)

\* Revised specifications and tests for the NDS.

Chemistry, Manufacturing and Controls Section  
FDA Form 356h, Item 3

IODINE CAPSULES  
200 mg, 300 mg

I. Drug Substance

D. Specifications and Analytical Methods for The Drug Substance  
(Formerly Paragraph 8.d.)

Unmicronized etodolac drug substance will meet the following specifications:

<u>Test</u> Description	<u>Specification</u> White to off-white crystalline powder	<u>Method</u> Visual
Identity (IR)	(b) (4)	(b) (4)
Identity (TLC)	(b) (4)	(b) (4)
Identity (HPLC)	(b) (4)	(b) (4)
Strength (HPLC)	(b) (4)	(b) (4)
Purity (TLC)	(b) (4)	(b) (4)
Methyl Analogs (HPLC)	(b) (4)	(b) (4)
Moisture (KF)	(b) (4)	(b) (4)
Residue on Ignition	(b) (4)	(b) (4)
Heavy Metals (II)	(b) (4)	(b) (4)
Residual Solvent	(b) (4)	(b) (4)
Methanol (GC)	(b) (4)	(b) (4)
(b) (4) (TLC)	(b) (4)	(b) (4)

After micronization in-house, the etodolac drug substance will meet the following specifications:

<u>Test</u> Description	<u>Specification</u> White to off-white crystalline powder	<u>Method</u> Visual
Identity (IR)	(b) (4)	(b) (4)
Identity (TLC)	(b) (4)	(b) (4)
Identity (HPLC)	(b) (4)	(b) (4)
Strength (HPLC)	(b) (4)	(b) (4)
Purity (TLC)	(b) (4)	(b) (4)
Moisture (KF)	(b) (4)	(b) (4)
Particle Size	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Note: The above specifications only reflect the addition of the (b) (4) specification and test.

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\* Analytical Method No. (b)(4) for determining (b)(4) in etodolac NDS by TLC.

TLC Method # (b)(4) describes the chromatographic conditions, equipment, reagents and materials used. The method also contains a detailed description of the procedure, including a typical TLC chromatogram.

System suitability specifications were submitted, showing the Rf value obtained for (b)(4) in the standard comparison solution chromatograms to be between (b)(4) and (b)(4) inclusive.

\* Suitability study (General Technical Report No. (b)(4) for the use of Method No. (b)(4).

A thin layer method has been developed to determine the presence of (b)(4) in etodolac NDS. The method has been shown to yield good resolution between the (b)(4) and etodolac active. Accuracy, and precision studies were performed on spiked and unspiked samples, ranging from (b)(4) concentration. According to the firm, the sensitivity of the method is capable of detecting as low as (b)(4). Accuracy and precision data were submitted; average recovery (b)(4). The precision of the method was shown to have a variance estimated at C.V. of (b)(4) between day and within day use (refer to tables II and III of supplement for data).

In conclusion, the TLC method is capable for the determination of the (b)(4) content in etodolac raw material. The method as shown is stability indicating and is suitable for its intended use.

The following chromatogram summarizes the capability of this TLC procedure to separate related compounds and the (b)(4) from etodolac:

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FIGURE 2  
SPECIFICITY OF METHOD 2992-180 FOR THE (b) (4)  
CHROMATOGRAM OF STRESSED SAMPLES OF ETODOLAC



The following compounds apply to the spiked sample



Note: The Rf's for these compounds were <sup>not</sup> indicated for this typical chromatogram; should be requested.

\* Summaries and abstracts of toxicology studies using etodolac drug substance (AY-24,236) containing (b) (4) of (b) (4) previously submitted to the Agency noted (see firm's letter, page 2).

This information should be referred to the pharmacologist (HFD-007).

cc: Orig. NDA #18-922	HFD-007/Yaciw	HFD-102
HFD-007/Div. File	HFD-007/Owens	
HFD-007/Pappas	HFD-340	