CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20535

ADMINISTRATIVE DOCUMENTS

NDA No.

PATENT INFORMATION UNDER SECTION 505(b)

In the opinion of applicant and to the best of applicant's knowledge, there is now no U.S. Patent which claims the drug referred to in this application or which claims a use of the drug for which the applicant is seeking approval.

WYETH-AYERST LABORATORIES

By: 

Robert Wiser
Chief Patent Counsel

PATENT/EXCLUSIVITY INFORMATION

1)	Active Ingredient	Bromfenac
2)	Strength(s)	25 and 50 mg capsules
3)	Trade Name	
4)	Dosage Form (Route of Administration)	Oral
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	20-535
7)	Approval Date	
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be submitted prior to 5 years after the date of approval of this NDA.
9)	Applicable patent numbers and expiration date of each	None

EXCLUSIVITY SUMMARY for NDA # 20-535 **SUPPL #** _____

Trade Name Duract **Generic Name** Bromfenac Sodium

Applicant Name Wyeth-Ayerst **HFD-** 550

Approval Date July 15, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.").

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS N/A

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✓/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

N/A (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

N/A (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /_✓_/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # YES /_✓_/ ! NO /___/ Explain: _____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

Chris Koerner
Signature
Title: Project Manager

July 15, 1996
Date

Signature of Division Director

8/22/96
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

BROMFENAC SODIUM
NDA 20-535

GENERIC DRUG ENFORCEMENT ACT OF 1992
CERTIFICATION STATEMENT

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 connection with NDA 20,535 for Bromfenac Sodium.

Signed: _____ Date: 10/19/94

Joseph M. Bathish,
Vice President
Worldwide Regulatory Affairs

PEDIATRIC PAGE

[Complete for all original applications and all efficacy supplements]

NDA/PLA # 20-535 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-550 Trade [generic] name/dosage form: ~~Bromfenac Sodium~~ _____ Action: AP AE NA

Applicant Wyeth Ayerst Therapeutic Class NSAID

Indication(s) previously approved None

Pediatric labeling of approved indication(s) is adequate ✓ inadequate ~~✓~~

Indication in this application Pain Relief.

(For supplements, answer the following questions in relation to the proposed indication.)

__ 1. PEDIATRIC LABELING IS ADEQUATE. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

__ 2. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use. is needed, and applicant has agreed to provide the appropriate formulation.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
___(1) Studies are ongoing.
___(2) Protocols were submitted and approved.
___(3) Protocols were submitted and are under review.
___(4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 3. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

__ 4. EXPLAIN. If none of the above apply, explain, as necessary on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Chin Koerner
Signature of Preparer and Title (PM, CSO, MO, other)

July 15, 1996
Date

cc:
Orig. NDA/PLA# 20-535
HFD-550 /Div.File
NDA/PLA Action Package
HFD-510/GTroendle(plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

Office Director's Memorandum on NDA 20-535

NDA #20-535

Review Completed: 7/16/97

Generic name:	Bromfenac Sodium Capsules
Proposed trade name:	Duract
Sponsor:	Wyeth Ayerst Labs
Pharmacologic Category:	Nonsteroidal Anti-Inflammatory
Proposed Indication(s):	Short term (generally less than 10 days) management of pain.
Dosage Form(s):	Oral capsules
NDA Drug Classification:	1 S
Issue:	**CMC Inspection - Lonza**

In the routine Philadelphia district's field inspection of bromfenac sodium manufacturer, the investigator found a number of GMP violations. We focused on one particular batch, number which was used in the biostudy bridging the material in the clinical studies to the "market image". Our chemists, Bart Ho and Hasmukh Patel, reviewed the data.

They checked the inspector's observation #5 that the lot was left in the dryer overnight. The chemists felt that this was not critical because the firm searched for polymorphs and none were detected in bromfenac recrystallized from water.

The second factor they checked was potency and degradation. The chemists felt that degradation was not a problem for this batch.

The eighteen months stability data for the batch had to be checked. They found it stable for the eighteen months studied. Degradation products were minimal to almost none. The retesting date for the batches is one year.

Of the drug product made with this bromfenac batch the specifications were acceptable. The results for assays, dissolution, degradation, and all other parameters were felt to be reasonable. These data were provided in the original application and the amendment.

They, Dr. Patel and Dr. Ho, have recommended to the firm that a limit for total quantities of degradation products present in the drug product be established.

The inspector's observation #2, that seven retests were done and that there was no further investigation for the thirty-six month stability sample for bromfenac sodium lot in question. The seven retests were within specifications and the thirty-six month stability data was not relevant. The firm is currently requesting a twelve month retest date. The melting points in solubility as well as intrinsic dissolution rates were fine.

In conclusion, the non GMP conditions have not affected the quality and purity of this batch of bromfenac drug substance manufactured by It met all the quality and purity specifications established in the NDA. The biostudy, therefore, performed with the drug product using this batch was acceptable. The drug substance had appropriate controls for moisture content and particle size, and has no polymorphs. There is no need for a biostudy to check for the change in its source.

Since the chemists feel there is no problem with this product I overrule Dr. Chambers' memo of 6/13/97.

MWeintraub 7/15/97

Michael Weintraub
Office Director
Office of Drug Evaluation V

cc: HFD-550
HFD-105/Weintraub
HFD-2/Lumpkin
HFD-340
HFD-550/PM/Koerner
HFD-550/TL/Hyde
HFD-550/CHEM/Ho/Patel
HFD-880/BIOPHARM/Bashaw
HFD-550/Chambers

NDA 20-535 Bromfenac sodium capsules

Executive Summary of Clinical Findings for Bromfenac NDA 20-535

- Single dose studies provide substantial evidence of an analgesic effect of the 25 mg dose. In fact, doses as low a 5 mg had analgesic activity. Given fasted, no higher dose surpassed 25 mg in the first 3 hours, but higher doses tended to extend the effect slightly.

- Bromfenac 25 mg was more effective than 650 mg of aspirin in dental pain models. Also, bromfenac 25 mg fasted was generally comparable to ibuprofen 400 mg and naproxen sodium 550 mg.

- The onset of analgesia with bromfenac 25 mg fasted was within 30 minutes, making it a suitable acute analgesic. The duration of action (median remedication time) was at least 6 hours. It is noteworthy that the analgesic effect lasted much longer than the plasma concentrations.

- There is a substantial food effect on the absorption of bromfenac: taking it with food reduces total bioavailability to less than half of the fasted value. One dental pain model showed that food significantly reduced the analgesic efficacy of a 25 mg dose, but that 50 mg with food was almost as effective as 25 mg fasted.

- Of three dysmenorrhea studies, two were disqualified after DSI inspections. The third study used bromfenac 10 mg and 50 mg, but not 25 mg. The review team recommends that the dysmenorrhea indication not be permitted until additional studies are done.

- The NDA lacked sufficient long-term follow-up to support OA or RA indications. Bromfenac did appear to have an effect in the OA population

- The profile of common adverse events, as well as PUBs (perforations, ulcers or bleeds), resembles that of most other NSAIDs. However, there appears to be significant hepatotoxcity. The rate of mild liver enzyme elevations was not unusual, but the incidence of significant liver enzyme elevations appeared to be relatively high. Some significant elevations occurred at about a month after starting bromfenac. The review team recommends that treatment with bromfenac be limited to 2 weeks.

- The proposed labeling recommended 200 mg as the maximum daily dose. Only about 200 patients were exposed chronically to a dose of that magnitude or higher. The review team recommends the maximum daily dose be set at 150 mg.