CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-944

ADMINISTRATIVE DOCUMENTS

Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-0871
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WHITEHALL ROBINS

December 19, 1997

Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-994
Advil® Chewable Tablets
(ibuprofen chewable tablets, 50 mg and 100 mg)
Patent and Exclusivity Information

Dear Sir/Madam:

Reference is made to our NDA submission herewith for (Children's and Jr. Strength) Advil® Chewable Tablets (ibuprofen chewable tablets, 50 mg and 100 mg), the requirements of the Federal Food, Drug, and Cosmetic Act ("Act") to submit patent and exclusivity information and the Food and Drug Administration ("FDA") interpretations of those sections of the Act. This new drug application also refers in part to NDA 20-589 for Children's Advil® Suspension (OTC) (approved 6/27/96) sponsored by Whitehall-Robins Healthcare. This submission supports a New Dosage Form for a line extension for over-the-counter ibuprofen. Please note that further reference is made, in part, to the following applications:

[redacted]	Ibuprofen Pediatric Chewable Tablets (Whitehall-Robins Healthcare)
NDA 20-812	Pediatric Advil® Drops (Whitehall-Robins Healthcare)
NDA 20-267	Junior Strength Advil® Tablets (Whitehall-Robins Healthcare)
NDA 19-833	Children's Advil® Suspension (Rx) (American Home Products Corp.)
NDA 19-784	Rufen® Pediatric Suspension (Boots Pharmaceutical Inc.)
NDA 18-197	Rufen® Tablets (Boots Pharmaceutical Inc.)

Patent Information-Updated

The undersigned certifies that the formulation or composition of ibuprofen chewable tablets, which product is the subject of this application, is claimed by U.S. Patent Number 5,563,993. The patent is assigned to Eurand America, Inc., a wholly owned subsidiary of American Home Products Corporation ("AHP"); Whitehall-Robins is a division of AHP and is also licensed by Eurand under the '993 patent.

Paragraph IV Certification

Whitehall-Robins certifies that U.S. Patent No. 5,563,993 will not be infringed by the manufacture, use or sale of (Children's and Jr. Strength) Advil® Chewable Tablets, i.e., the product(s) which is/are the subject of this application. Whitehall-Robins has complied with the requirements of 21 CFR 314.552(a) with respect to providing a notice of this certification to the patent owner, Eurand. Note that Whitehall-Robins has been granted a patent license by the patent owner. In lieu of providing any further notice, attached as Exhibit C is a letter from Eurand America, Inc., waiving their right to receive any further notice.

Exclusivity Information-Updated

New Clinical Investigation

1) This submission relies primarily on a new clinical investigation in humans conducted under Whitehall-Robins [redacted] described below:

AF-95-06 Comparative Evaluation of the Antipyretic Efficacy and Safety of Ibuprofen 50 mg Chewable Tablets and Ibuprofen 20 mg/ml Suspension in Children

Philip D. Walson, MD
Children's Hospital
Columbus, Ohio

Jeffery L. Blumer, MD, PhD
Rainbow Babies and Children's Hospital
Cleveland, Ohio

Thomas G. Wells, MD
Arkansas Children's Hospital
Little Rock, Arkansas

John T. Wilson, MD
Louisiana State University Medical Center
Shreveport, Louisiana

Richard Buchta, MD
Scripps Clinic
La Jolla, California

Russell W. Chesney, MD
LeBonheur Children's Medical Center
Memphis, Tennessee

John H. Bornhofen, MD
Clinical Investigations Specialists, Inc.
Little Rock, Arkansas

With respect to the above-identified investigations,

The undersigned certifies, that to the best of her knowledge, the investigation identified hereinabove have formed part of the basis of a finding of substantial evidence of effectiveness for this indication in a previously approved new drug application.

Essential to Approval

2) With respect to the FDA's interpretation that the new clinical investigation is essential to approval,

The undersigned certifies that the scientific literature has thoroughly been searched and, to the best of the undersigned's knowledge, attached as Exhibit B is a complete and accurate list (as of December 1997) of published studies or publicly available reports generated with respect to the use of the ibuprofen active ingredient in children, which relates to the product which is the subject of this new drug application.

In the opinion of the undersigned, there are not sufficient published or publicly available reports of clinical evaluations to support the approval of (Children's and Jr. Strength) Advil® Chewable Tablets (ibuprofen chewable tablets, 50 mg and 100 mg), other than that conducted and sponsored by the applicant.

Conducted or Sponsored by the Applicant

3) In regards to the undersigned-sponsored study identified in paragraph 1) above,

The undersigned certifies, that applicant sponsored the study identified above in paragraph 1) by providing more than 50% of the cost of conducting each said study.

Applicant is the sponsor named in each Form FDA 1571 for each study identified in paragraph 1) as well as the sponsor named in the IND.

Exclusivity Rationale

Whitehall-Robins is seeking a three year period of exclusivity as provided in the Act for Advil® Chewable Tablets (ibuprofen chewable tablets, 50 mg and 100 mg) for the indication of the temporary reduction of fever and relief of minor aches and pains due to common cold, flu, sore throat, headaches, and toothaches.

The study outlined above, sponsored by the applicant, include significant, new clinical investigations "other than bioavailability studies" as required for NDA approval and are precisely what are referred to in the statute as "essential to the approval of the application."

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Sharon Heddish

Sharon C. Heddish
Vice President, Regulatory Affairs Worldwide

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 20-944 SUPPL #

Trade Name Advil Chewable Tablets, 50 mg and 100 mg

Generic Name Ibuprofen tablets

Applicant Name Whitehall-Robins Healthcare HFD # 550

Approval Date If Known

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 question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

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 /X/

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.

The purpose of study AF-95-016 was to show that the slower absorption rate did not translate into clinically detectable slower antipyretic effect compared to the approved suspension.

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:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

__ YES /X/ NO /___/

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

e) Has pediatric exclusivity been granted for this Active Moiety?

No

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? (Rx to OTC switches should be answered NO-please indicate as such)

YES /X/ NO /___/

If yes, NDA #20-601. Drug Name Children's Motrin (ibuprofen tablets) 50 mg and Junior Strength Motrin (ibuprofen tablets) 100 mg.

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.

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

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 "ves" 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.

(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: _____

_____

(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: _____

_____

(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:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /___/

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

_____ _____

_____ _____

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 /___/

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

_____ _____

_____ _____

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"):

_____ _____

_____ _____

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?

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: _____

_____

/S/ 12/10/98
Signature Date
Title: Project Manager

/S/ 12-16-98
Signature of Office/ Date
Deputy Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20944	**Trade Name:**	ADVIL (IBUPROFEN) ~~10MG~~ 100mg/50MG CHEWABLE TABS
Supplement Number:		**Generic Name:**	IBUPROFEN
Supplement Type:		**Dosage Form:**	Tablet, Chewable; Oral
Regulatory Action:	AP	**Proposed Indication:**	

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? YES

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) _X_Children (25 months-12 Years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status	ADEQUATE Labeling for SOME PEDIATRIC ages
Formulation Status	NEW FORMULATION developed with this submission
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, SANDRA COOK

Signature /S/ _____ Date 12/18/98

APPEARS THIS WAY
ON ORIGINAL

Whitehall-Robins Healthcare
Madison, New Jersey

New Drug Application # 20-944
Advil® Chewable Tablets
(ibuprofen 50mg, 100mg)

Debarment Statement

Whitehall-Robins, to the best of its knowledge, did not and will not use in any capacity the services of any person debarred under sections 306 of the act in connection with such application

Sharon Heddish

Sharon Heddish
Vice President
Regulatory Affairs Worldwide
Whitehall-Robins Healthcare

CDER Establishment Evaluation Report for November 12, 1998

Application: NDA 20944/000
Stamp: 22-DEC-1997 Regulatory Due: 22-DEC-1998
Applicant: WHITEHALL ROBINS
5 GIRALDA FARMS
MADISON, NJ 079400871

Priority: 3S Org Code: 550
Action Goal: District Goal: 22-AUG-1998
Brand Name: ADVIL (IBUPROFEN)10MG/50MG CHEWABLE TABS
Established Name:
Generic Name: IBUPROFEN
Dosage Form: TAB (TABLET)
Strength: 100 MG AND 50 MG

FDA Contacts:			
S. COOK	(HFD-550)	301-827-2090	, Project Manager
B. HO	(HFD-550)	301-827-2050	, Review Chemist
H. PATEL	(HFD-550)	301-827-2507	, Team Leader

Overall Recommendation:

ACCEPTABLE on 13-JAN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 12-JAN-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: 1525864
EURAND AMERICA INC
845 CENTER DR
VANDALIA, OH 45377

DMF No: [redacted]
AADA No:

Profile: CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 12-JAN-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: [redacted]
DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 12-JAN-1998

Responsibilities: FINISHED DOSAGE PACKAGER

Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 12-JAN-1998
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 12-JAN-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY-TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 12-JAN-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: TCM **OAI Status:** NONE

Responsibilities: FINISHED DOSAGE

MANUFACTURER

Last Milestone: OC RECOMMENDATION
Milestone Date 13-JAN-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION