CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-944

CORRESPONDENCE

Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-0871
Telephone (973) 660-5500
Website address: http://healthfront.com

WHITEHALL ROBINS

December 19, 1997

NDA 20-944
Advil® Chewable Tablets
(ibuprofen 50mg, 100mg)

Micheal Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-105)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Dear Mr. Weintraub:

Pursuant to section 505 (b) of the Federal Food, Drug and Cosmetic Act and in accordance with 21CFR part 314.50, Whitehall-Robins Healthcare ("Whitehall-Robins"), a Division of American Home Products ("AHP"), is hereby submitting a New Drug Application ("NDA") to provide for over-the-counter marketing of Advil® Chewable Tablets, (ibuprofen 50mg, 100mg) as a line extension to currently marketed Children's Ibuprofen products (Children's Advil® Suspension and Junior Strength Advil® Tablets).

Advil® Chewable Tablets, (ibuprofen 50mg, 100mg) will be marketed for children ages 2-11 for the following indications:

- Temporarily reduces fever

- Temporarily relieves minor aches and pains due to the common cold, flu, sore throat, headaches and toothaches.

These indications are identical to those of currently approved over-the-counter ibuprofen suspension (ages 2-11) and swallowable tablet (ages 6-11) formulations, NDA 20-589 Children's Advil Suspension) and NDA 20-267 (Junior Strength Advil Tablets), respectively.

This application contains studies conducted [redacted] Early prototype ibuprofen chewable tablet formulations were evaluated in three pilot bioavailability studies. The final Advil Chewable formulation was evaluated in bioavailability study AF-95-03 entitled, *"A Randomized, Single-Dose, Four-Way Crossover, Bioequivalence Food Effects Study Evaluating Whitehall-Robins Advil® (ibuprofen)100mg Chewable Tablets."* The results of AF-95-03 demonstrated bioequivalence between Advil® Chewable tablets and the approved Junior Strength Advil® Tablet formulations, but not between the Advil® Chewable Tablet and Children's Advil® Suspension formulation.

Whitehall-Robins Healthcare sought input from the agency regarding acceptance of filing a New Drug Application for the chewable tablet product based upon showing bioequivalence to the approved Junior Strength Advil® Tablet. The agency recommended that approval for the product would require clinical data demonstrating that a later Tmax (vs that seen with Children's Advil® Suspension) is not clinically relevant.

Thus, with this guidance from the Agency, the NDA includes clinical data from a fever study AF-95-06 entitled *"Comparative Evaluation of Antipyretic Efficacy and Safety of Ibuprofen 50mg Chewable Tablet and Ibuprofen 20mg/Ml Suspension in Children."*

Whitehall-Robins certifies that a field copy of the Chemistry, Manufacturing and Controls section of this NDA will be forwarded to the FDA District Offices in North Brunswick, New Jersey and Buffalo, New York, respectively.

Additionally, under separate cover, a check (User Fee ID 3368) [redacted] has been submitted. We understand through a December 15, 1997 telephone discussion with Mr. Tom Hassall, and the recent Federal Register Notice (published December 9, 1997) that FDA will invoice Whitehall-Robins accordingly for the adjusted portion of the remaining User Fee.

If you have any questions or comments regarding this submission, please contact Ms. Joanne Robinett at 973-660-6167 or the undersigned at 973-660-5753.

Sincerely,

Sharon Heddish

Ms. Sharon Heddish
Vice President, Regulatory Affairs Worldwide

DUPLICATE

BC

ORIG AMENDMENT

Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-0871
Telephone (973) 660-5500
Website address: http://healthfront.com

February 12, 1998

NDA 20-944
Advil® Chewable Tablets
(ibuprofen 50 mg, 100 mg)

RESPONSE TO FDA REQUEST FOR INFORMATION

Michael Weintraub, MD, Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-105)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN.: Document Control Room N115
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Weintraub:

Reference is made to NDA 20-944 for Advil Chewable Tablets sponsored by Whitehall-Robins Healthcare, ("Whitehall-Robins"), a division of American Home Products Corporation. On February 5, 1998, Ms. Sandra Cook of the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, called to inform us that a request had been made for a statement indicating that we would be prepared for a Pre-Approval Inspection within six months of the filing of the Application.

Per that request, attached herewith please find the document prepared with the statement requested.

Should you have any comments regarding this submission or need additional information, please contact the undersigned at (973) 660-5753 or Joanne Robinett at (973) 660-6167.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Sharon Heddish

Sharon Heddish
Vice President,
Regulatory Affairs Worldwide

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ORIG AMENDMENT

ORIGINAL

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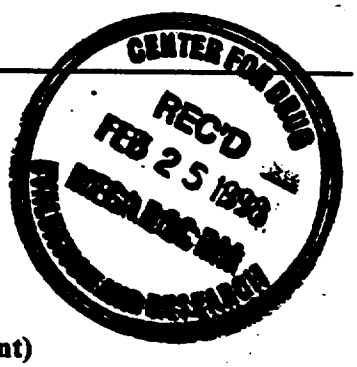

February 23, 1998

NDA 20-944
Advil® Chewable Tablets
(ibuprofen 50 mg, 100 mg)

Response to FDA Request for Claim of Categorical Exclusion:
Chemistry, Manufacturing and Controls (Environmental Assessment)

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-105)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Weintraub:

Reference is made to pending NDA 20-944 for Advil® (ibuprofen) Chewable Tablets submitted December 19, 1997 and sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins"), a Division of American Home Products Corporation. Specific reference is made to the Chemistry, Manufacturing and Controls section (Item 3) of NDA 20-944 which contained a full Environmental Assessment. Further reference is made to a February 17, 1998 telephone conversation between Ms. Nancy Sager (FDA) and Ms. Susan Beavis (Whitehall-Robins), during which FDA advised that the chemistry reviewer (Bart Ho) had requested a Claim of Categorical Exclusion for NDA 20-944 in accordance with 21 CFR 25.15(d) and during which FDA explained that an appropriate citation would be 21 CFR 25.31(a).

In response to FDA's request, Whitehall-Robins is providing a Claim of Categorical Exclusion relative to the Environmental Assessment citing 21 CFR 25.31(a). We trust that the information contained in this amendment will facilitate a continued review of our pending NDA application. If you have any questions regarding the enclosed information, please contact Mr. Vin Milano [phone 973-660-6160, fax 973-660-7184].

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Susan Beavis
for Vin Milano
Senior Director, Regulatory Affairs

BC

ORIG AMENDMENT

DUPLICATE

Whitehall-Robins
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March 20, 1998

NDA 20-944
Advil® Chewable Tablets
(ibuprofen 50 mg, 100 mg)

Amendment to a Pending Application

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-105)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Weintraub:

Reference is made to pending NDA 20-944 for Advil® (ibuprofen) Chewable Tablets submitted December 19, 1997 and sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins"), a Division of American Home Products Corporation. This amendment updates certain information submitted in NDA 20-944 as follows:

- A report is enclosed which explains and corrects minor errors in certain dissolution tables and graphs. Please note that the errors had no effect on any conclusions reached from examination of the dissolution data.
- A revised facilities listing is enclosed which reflects that accelerated stability storage and physical testing will move from Hammonton, NJ to Richmond, VA. Please note that this move is a consequence of Whitehall-Robins' decision to close our Hammonton, NJ R&D facility during 1998. Also note that Whitehall-Robins has already contacted FDA's Baltimore District Office to discuss our relocation plans. Please be assured that we will continue to keep the District informed of our activities related to this move so that appropriate inspections can be scheduled and conducted as necessary.
- A page of stability results is enclosed which was inadvertently omitted from the original NDA submission during the automated pagination process and which was regrettably not detected during our quality check of the NDA prior to submission.

Whitehall-Robins Healthcare
Amendment to a Pending Application
March 20, 1998

NDA 20-944
Advil® Chewable Tablets
(ibuprofen 50, 100mg)

We trust that the information contained in this amendment will facilitate a continued review of our pending NDA application. If you have any questions regarding the enclosed information, please contact the undersigned [phone 973-660-6160, fax 973-660-7162].

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Susan Beavis

for Vin Milano
Senior Director, Regulatory Affairs

WHITEHALL ROBINS

Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-0871
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NC
NEW CORRESP
ORIGINAL

April 17, 1998

NDA 20-944
Advil® Chewable Tablets
(ibuprofen, 50mg, 100 mg)

ITEM 9 - Safety Update

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-105)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Weintraub:

Reference is made to NDA 20-944 Advil® Chewable Tablets, (ibuprofen, 50mg, 100 mg) sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins"), a Division of American Home Products which was submitted on December 12, 1996.

Pursuant to 21CFR 314.50(d)(5)(vi)(b)(1), please note there is no new safety information to report that may reasonably affect the statement of contraindications, warnings, precautions and/or adverse reactions of the labeling. Therefore, Safety Update is not required at this time.

If you have any questions or comments regarding this information, please do not hesitate to contact the undersigned at (201) 660-5753 or Mr. Ron Guido at (201) 660-6662.

Sincerely,
WHITEHALL-ROBINS HEALTHCARE

Sharon Heddish
Vice President, Worldwide Regulatory Affairs

JC
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WHITEHALL ROBINS

NAF
VIN
7/14/98

July 16, 1998

NDA 20-944
Advil® Chewable Tablets
(ibuprofen 50 mg, 100 mg)

Amendment to a Pending Application

John Hyde, Ph. D., M.D., Deputy Director
Division of Anti-Inflammatory/Analgesic (HFD-505)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Hyde,

Reference is made to pending NDA 20-944 for Advil® (ibuprofen) Chewable Tablets submitted December 19, 1997 and sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins"), a Division of American Home Products Corporation. In response to the Division's 7/10/98 telephone request for chemistry information, the documentation pertaining to ~~Eurand's~~ [redacted] Content were forwarded to S. Cook (CSO) on July 14, 1998 via facsimile. We are hereby submitting to the NDA a copy of the documentation provided via facsimile on July 14, 1998 (in triplicate).

We trust that the information contained in this amendment will facilitate a continued review of our pending NDA application. If you have any questions regarding the enclosed information, please contact the undersigned, phone (973)-660-6160, fax (973)-660-7162 or Susan Beavis at (973) 660-5068.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Susan Beavis

for Vin Milano
Senior Director, Regulatory Affairs

ORIGINAL

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

BE

November 10, 1998

NDA 20-944
Advil® Chewable Tablets
(ibuprofen 50 mg, 100 mg)

Amendment to a Pending Application

Debra Bowen, M.D., Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Hyde,

Reference is made to pending NDA 20-944 for Advil® (ibuprofen) Chewable Tablets submitted December 19, 1997 and sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins"), a Division of American Home Products Corporation. Reference is also made to our November 10, 1998 telephone conversation with the Division, during which the chemistry reviewer (Bart Ho) advised Whitehall-Robins (Ken Warner and Susan Beavis) to withdraw the "Protocol for Establishing Equivalence of Packaging Components" (pages 03-00813 and 03-00814) from the NDA. In accordance with the Division's recommendation, Whitehall-Robins hereby withdraws the "Protocol for Establishing Equivalence of Packaging Components" from NDA 20-944 in order to facilitate and bring closure to the chemistry review of this pending application.

If you have any further questions, please contact the undersigned [phone 973-660-6896, fax 973-660-7162] or Susan Beavis [phone 973-660-5068, fax 973-660-5919].

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Susan Beavis

Ken Warner
Associate Director, Regulatory Affairs

c.c.: Bart Ho (FDA)

WHITEHALL ROBINS

Whitehall-Robins

5 Giralda Farms

Madison, NJ 07940

FAX

TO: Bart Ho, FDA

DEPT: Division of Anti-Inflammatory, Analgesic & Ophthalmic Drug Products

FAX: 301-827-2531

FROM: Susan Beavis

DEPT: Regulatory Affairs

FAX NO: 973-660-5919

PHONE NO: 973-660-5068

DATE: November 10, 1998

NUMBER OF PAGES (including cover sheet): 2

Please find attached a copy of an amendment to pending NDA 20-944 for Advil (ibuprofen) Chewable Tablets, which complies with your recommendation to withdraw the "Protocol for Establishing Equivalence of Packaging Components" from the application. We understand that this action will facilitate and bring closure to the chemistry review of our pending NDA. Please advise if any further information is required.

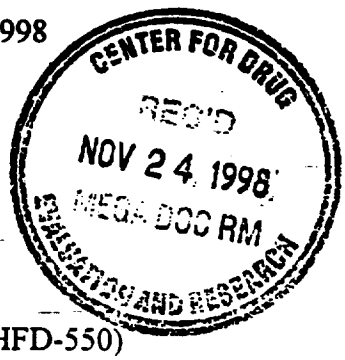
Susan Beavis

NDA ORIG AMENDMENT ORIGINAL

Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-0871
Telephone (973) 660-5500
Website address: http://healthfront.com

WHITEHALL ROBINS

November 20, 1998



NDA 20-944
Advil® Chewable Tablets
(ibuprofen 50 mg, 100 mg)

Response to Division Facsimile dated 11/13/98 (Chemistry Comments)

Debra Bowen, M.D., Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

SUMMARY

Dear Dr. Bowen,

Reference is made to pending NDA 20-944 for Advil® (ibuprofen) Chewable Tablets submitted December 19, 1997 and sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins"), a Division of American Home Products Corporation. Reference is also made to the Division's November 13, 1998 facsimile (copy attached), which contained comments on the Chemistry section of the NDA. Please find enclosed Whitehall-Robins' response to the Division's November 13, 1998 Chemistry comments. We trust that this response will satisfactorily address all issues relative to this pending application and bring closure to the review process.

If you have any further questions, please contact the undersigned [phone 973-660-6896, fax 973-660-7162] or Susan Beavis [phone 973-660-5068, fax 973-660-5919].

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Susan Beavis

Ken Warner
Associate Director, Regulatory Affairs

c.c.: Bart Ho, FDA (desk copy)
S. Cook, FDA (cover letter)