CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-587

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY AND TOXICOLOGY COVER SHEET

NDA number: 21-587
Review number: 001
Sequence number/date/type of submission: 000/April 24, 2003/Initial NDA
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Whitehall-Robins Healthcare

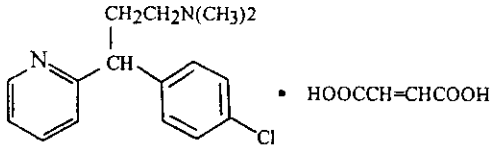
Reviewer name: María I. Rivera
Division name: Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD #: 550
Review completion date: October 27, 2003

Drug:

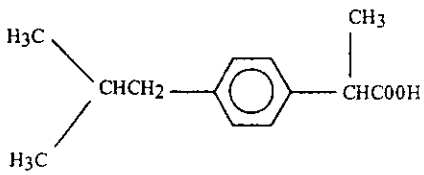
Trade name: Children's Advil® Allergy Sinus Suspension/ [redacted]

Components

Generic name: Chlorpheniramine maleate
Chemical name: 2-pyridinepropanamine, γ-(4-chlorophenyl)-N,N-dimethyl-,(Z)-2-butenedioate (1:1)
CAS registry number: 113-92-8
Molecular formula/molecular weight: $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$/390.86
Manufacturer: [redacted]
Structure:

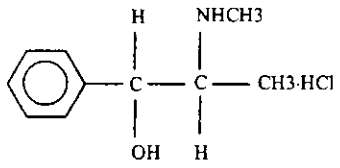


Generic name: Ibuprofen
Chemical name: (±)-2-(p-isobutylphenyl)propionic acid or (R,S)-2-(4-isobutyl-phenyl)-propionic acid
CAS registry number: 15687-27-1
Molecular formula/molecular weight: $C_{13}H_{18}O_2$/206.28
Manufacturer: [redacted]
Structure:



Generic name: Pseudoephedrine hydrochloride
Chemical name: (+)-α-[1-(methylamino)ethyl]benzenemethanol hydrochloride
CAS registry number: 345-78-8
Molecular formula/molecular weight: $C_{10}H_{15}NO \cdot HCl/201.69$
Manufacturer: [redacted]

Structure:



Relevant INDs/NDAs/DMFs:

NDA 18-989 Advil Tablets, Caplets, Gelcaps (200 mg)
NDA 20-402 Provel™ (Advil) Liquigels (200 mg)
NDA 20-589 Children's Advil Suspension (100 mg/5 ml)
NDA 20-267 Junior Strength Advil Tablets (100 mg)
NDA 20-812 Pediatric Advil Drops (100 mg/2.5 ml)
NDA 20-944 Children's (50 mg) and Jr. Strength (100 mg) Advil Chewable Tablets

Combination tablet 200 mg ibuprofen/30 mg pseudoephedrine hydrochloride:
NDA 19-771 Advil Cold & Sinus Tablets/Caplets
NDA 21-374 Advil Cold & Sinus Liquigels (pending)
IND 25,532 Ibuprofen 200 mg/pseudoephedrine HCl 30 mg

Combination suspension 100 mg ibuprofen/15 mg pseudoephedrine hydrochloride/5 ml:
NDA 21-373 Children's Advil Cold Suspension

Combination caplet 200 mg ibuprofen/30 mg pseudoephedrine hydrochloride/2 mg chlorpheniramine maleate:
IND 61,725 Advil Multisymptom Allergy Sinus
IND 63,999 Children's Advil Allergy Sinus Suspension
NDA 21-441 Advil Allergy Sinus Caplets

DMF # [redacted]
DMF # [redacted]
DMF # [redacted]

Drug class: analgesic/decongestant/antihistamine

Indication: Temporary relief of symptoms associated with hay fever or other upper respiratory allergies and the common cold such as runny nose, sneezing, itching of the nose or throat, itchy, watery eyes, headache, minor aches and pains, and nasal congestion in children 6 to < 12 years of age.

Clinical formulation: Will be prepared — flavors: ——— ' berry.

flavored formulation:

Component	% w/v (theoretical)	mg/teaspoon (5 ml)
Ibuprofen USP		100
Pseudoephedrine HCl USP		15.0
Chlorpheniramine Maleate USP		1.00
Xanthan Gum NF Pharm.		
Microcrystalline Cellulose		
Polysorbate 80 NF		
Glycerin		
Sorbitol Solution USP		
Sucralose		
Sodium Citrate USP/		
Sodium Benzoate NF		
Edetate Disodium USP		
Citric Acid		
Flavor Artificial		
FD&C Red No. 40		
FD&C Blue No. 1		
Purified Water USP		

Bubblegum flavored formulation contains similar ingredients as above with the following modifications:

Component	% w/v (theoretical)	mg/teaspoon (5 ml)
flavor artificial		
No FD&C Blue No. 1		

Route of administration: oral

Proposed use: Directions for use indicate administering 2 teaspoons (10 ml)/dose, and a maximum of 4 doses/day for children age 6-11 years (48-95 lbs.). Maximum recommended daily dosing for individual ingredients would be 800 mg ibuprofen, 120 mg pseudoephedrine and 8 mg chlorpheniramine.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise. Part of the text is from Sponsor's submission.

Studies reviewed within this submission: No nonclinical studies were submitted.

Studies not reviewed within this submission: No nonclinical studies were submitted.

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability: Approval is recommended.

1.2 Recommendation for nonclinical studies: No additional nonclinical studies are necessary. Ibuprofen, chlorpheniramine maleate, and pseudoephedrine hydrochloride are currently approved OTC drugs as single ingredients or in combinations and the safety profile of each active ingredient is well established.

1.3 Recommendations on labeling: Not applicable

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings:

The Sponsor did not submit any nonclinical studies with the proposed ibuprofen/pseudoephedrine hydrochloride/chlorpheniramine maleate (200/30/2 mg/dose) combination to be used in children 6-11 years old (48-95 lbs). The safety and efficacy of ibuprofen, pseudoephedrine hydrochloride, and chlorpheniramine maleate have been demonstrated through extensive clinical testing and marketing experience. Combination products containing pseudoephedrine hydrochloride plus ibuprofen or chlorpheniramine maleate are currently marketed as OTC products for use in adults and children. The combination of ibuprofen and pseudoephedrine (200/30 mg) has been available OTC from Whitehall-Robins Healthcare since 1989 for use in adults and children 12 yr of age and older (Advil® Cold & Sinus Tablets/Caplets, NDA 19-771). More recently (Dec 2002), the adult counterpart of the proposed triple combination was approved (NDA 21-441, Advil Allergy Sinus Caplets).

The human pharmacokinetic data obtained during the program development for NDA 19-771 showed bioequivalence when ibuprofen/pseudoephedrine hydrochloride were given as a combination product or separately. The potential for interaction effects when a third active ingredient (chlorpheniramine) was added to the combination was evaluated in NDA 21-441 (Advil Allergy Sinus Caplets). The results from clinical trial AD-99-01 showed that the pharmacokinetic profiles of ibuprofen, pseudoephedrine, and chlorpheniramine were similar for individual versus combination administration. Based on C_{max} and AUCI (AUC from time 0 to infinity), the three active ingredients in Advil Allergy Sinus Caplets were absorbed at the same rate and to the same extent as the individual reference treatments, with confidence intervals that fell within the acceptable bioequivalence range.

In the current NDA two pharmacokinetic studies were submitted:

1. Study AR-00-02: The study consisted of a combination bioequivalence/food-effect study in adults where the systemic exposures of the caplet and suspension

formulations of the ibuprofen/pseudoephedrine hydrochloride/chlorpheniramine maleate combination under fed/fasted conditions were compared.

2. Study AR-00-03: This study was conducted to compare the total systemic exposure, of ibuprofen, pseudoephedrine hydrochloride, and chlorpheniramine maleate from the combination suspension when administered to children 6 to <12 years of age presenting with symptoms consistent with allergic rhinitis versus the systemic exposure obtained for the suspension in healthy adults.

The results of the pharmacokinetic studies conducted in support of the combination suspension demonstrated that food effects were not unexpected and of minimal clinical consequence (refer to biopharm review). Similarly, the formulation effects seen when the combination in suspension and caplet forms were compared are not likely to have clinical significance. Lastly, the AUC and C_{max} of each active ingredient in the suspension were not substantially different between allergy-symptomatic children 6 to <12 years of age and healthy adults.

Given that the clinical PK data showed no drug-drug interactions, the safety profile of each active ingredient is well established, and the doses proposed are within those of currently marketed products, preclinical studies to address the safety of the triple combination are not considered necessary.

In a fax dated February 20, 2002, the Agency requested that the Sponsor tighten the limits of the degradation product . ——————— to less than —— or to qualify the impurity. The specification has been tightened in accordance with ICH guidances (not more than —— w/w of pseudoephedrine HCl content), and therefore no toxicological assessment is warranted at this time.

2.2 Pharmacologic activity

No pharmacology studies were submitted with the proposed ibuprofen/ pseudoephedrine hydrochloride/chlorpheniramine combination. All three active ingredients have been studied extensively and the pharmacologic properties of the drugs are well known. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. Pseudoephedrine is an orally active indirect-acting sympathomimetic amine recognized as an effective agent for the temporary relief of nasal congestion due to the common cold, hay fever, other allergies, or sinusitis. Chlorpheniramine, a classical H_1-receptor antagonist, has been shown to be effective against major histamine-mediated symptoms, i.e., sneezing, itching, and rhinorrhea.

2.3 Nonclinical safety issues relevant to clinical use

None

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

The formulation proposed in this NDA is a suspension containing an analgesic, ibuprofen, a nasal decongestant, pseudoephedrine hydrochloride, and an antihistamine, chlorpheniramine maleate for use in children 6 to < 12 years of age. The safety and efficacy of ibuprofen, pseudoephedrine hydrochloride, and chlorpheniramine maleate have been demonstrated through extensive clinical testing and marketing experience.

Pseudoephedrine hydrochloride is considered GRASE for OTC use with dosing to 120 mg/day for children 6–11 years old (21 CFR 341.80(d)(1)(ii)). Chlorpheniramine maleate is also considered GRASE for OTC use with dosing to 12 mg/day for children 6-11 years old (21 CFR 341.72). Ibuprofen has been marketed for many years as a prescription and OTC drug product for use in adults and children. Ibuprofen is recognized as safe at doses up to 1200 mg/day and is currently under review for GRASE status. The Sponsor made reference to the following approved OTC New Drug Applications from Whitehall-Robins Healthcare products for information on clinical pharmacology, pharmacokinetics, and clinical trial data:

NDA 18-989 Advil Tablets, Caplets, Gelcaps (200 mg)
NDA 20-402 Provel™ (Advil) Liquigels (200 mg)
NDA 20-589 Children's Advil Suspension (100 mg/5 ml)
NDA 20-267 Junior Strength Advil Tablets (100 mg)
NDA 20-812 Pediatric Advil Drops (100 mg/2.5 ml)
NDA 20-944 Children's (50 mg) and Jr. Strength (100 mg) Advil Chewable Tablets

The combination of 200 mg ibuprofen/30 mg pseudoephedrine hydrochloride in a tablet form was the subject of the following Whitehall-Robins Healthcare applications:

NDA 19-771 Advil Cold & Sinus Tablets/Caplets
NDA 21-374 Advil Cold & Sinus Liquigels
IND 25,532 Ibuprofen 200 mg/pseudoephedrine HCl 30 mg

The combination of 100 mg ibuprofen/15 mg pseudoephedrine hydrochloride in suspension form was the subject of Whitehall-Robins Healthcare NDA 21-373, Children's Advil Cold Suspension.

The combination of 200 mg ibuprofen/30 mg pseudoephedrine hydrochloride/2 mg chlorpheniramine maleate in tablet form was the subject of Whitehall-Robins Healthcare NDA 21-441, Advil Allergy Sinus Caplets.

3.2 PHARMACOLOGY

Refer to the review of NDA 21-441.

3.3 PHARMACOKINETICS/TOXICOKINETICS

Refer to the review of NDA 21-441.

3.4 TOXICOLOGY

Refer to the review of NDA 21-441.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Given that the clinical PK data showed no drug-drug interactions, the safety profile of each active ingredient is well established, and the doses proposed are within those of currently marketed products, nonclinical studies to address the safety of the triple combination are not considered necessary.

In a fax dated February 20, 2002, the Agency requested that the Sponsor tighten the limits of the degradation product [redacted] to less than [redacted] or to qualify the impurity. The specification has been tightened in accordance with ICH guidances (not more than [redacted] w/w of pseudoephedrine HCl content), and therefore no toxicological assessment is warranted at this time.

Unresolved toxicology issues (if any): None

Recommendations: Approval is recommended.

Suggested labeling: Not applicable

Signatures:

Reviewer Signature _____
María I. Rivera, PhD

Supervisor Signature_____ Concurrence Yes ___ No ___
Josie Yang, PhD

3.7. APPENDIX/ATTACHMENTS

cc list:

NDA 21-587/Initial NDA
HFD-550/Division File
/J Dean/PM
/C Fang/MO
/J Yang/ Pharm-Tox TL
/MI Rivera/Pharm-Tox

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Maria I. Rivera
11/17/03 09:34:51 AM
PHARMACOLOGIST

Josie Yang
11/17/03 11:01:47 AM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL