CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-373

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21373
Review number: No. 1
Sequence number/date/type of submission: 000/June 18, 2001/original submission
Information to sponsor: Yes () No (x)
Sponsor and/or agent: Whitehall-Robins Healthcare.
Manufacturer for drug substance: Wyeth-Ayerst

Reviewer name: Conrad H. Chen, Ph.D.
Division name: The Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products.
HFD #: 550
Review completion date: February 8, 2002

Drug:
Trade name: Children's Advil Cold Suspension, for OTC
Generic name: Ibuprofen 100 mg/ Pseudoephdrine HCl 15 mg/5 ml
Code name:
Chemical name: Ibuprofen, Pseudoephedrine
CAS registry number:
Mole file number:
Molecular formula/molecular weight: $C_{13}H_{18}O_2$/206.27, $C_{10}H_{15}NO \bullet HCl$
Structure:

Relevant IND/NDA/DMF:
NDA 19771, Approved 8-19-89 (CoAdvil/Advil Cold & Sinus Tablets and Caplets).
——— (Children's Advil Cold & Sinus Suspension, Ibuprofen 110mg/ Pseudoephedrine 15 mg/5 ml).

Drug class: NSAID and Nasal Decongestant.
Indication: Temporary relief of cold, sinus and flu symptoms.
Clinical formulation:

Ingredient *	**% W/V**	**Per 5 mL unit dose (mg)**	**Per 1000 gallon batch (kg)**
Ibuprofen USP	2.00	100	76.0
Pseudoephedrine HCl USP	0.300	15.0	11.4
Xanthan Gum NF Pharm. Grade	———	———	
Microcrystalline Cellulose / CMC Sodium NF			

Carboxymethylcellulose Sodium	USP		
Polysorbate 80 NF			
Glycerin USP			
Sorbitol Solution 70% USP			
Sucrose Beet NF			
Sodium Benzoate NF			
Disodium Edetate USP			
Citric Acid Hydrous USP			
Artificial Grape Flavor			
FD&C Red No. 40			
FD&C Blue No. 1			
Purified Water USP	Qs 100%	Qs 5 mL	Qs 1000 gallons

Route of administration: Oral
Proposed use: Do not use more than 4 times a day (every 6 hrs. if needed).
Under 2 yr., ask a doctor; 2-5 yr., 1 teaspoon (5ml); 6-11 yr., 2 teaspoon (10ml).
Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Recommend approval.

B. Recommendation for Nonclinical Studies
None.

C. Recommendations on Labeling
Since this is an OTC product, there is no labeling issue regarding the Pregnancy Section.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings
The mouse teratology study (#3199.2) is submitted. Together with previous submission of rat teratology study (#3199.1, under NDA 19771, dated 1-29-88), the sponsor has fulfilled the Phase IV commitment previously made. The fetal findings in these studies were all negative.

B. Pharmacological Activity
NSAID and nasal decongestant.

C. Nonclinical Safety Issues Relevant to Clinical Use
The sponsor referred to the approved NDA 19771 for the nonclinical safety information. The subject of NDA 19771, CoAdvil, has been marketed since 1989.

III. Administrative

A. Reviewer signature:

Conrad H. Chen, Ph. D.

B. Supervisor signature: Concurrence-

Non-concurrence-
(see memo attached)

B. cc: list:
HFD-550 MO/ Fang
HFD-550 Chem/ Ho
HFD-550 Pharm/ Chenco
HFD-550 PharmTL/ Yang

TABLE OF CONTENTS-PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I-VI. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY:

Reference is made to NDA 19711, CoAdvil/Advil Cold & Sinus Tablets and Caplets, submitted September 1, 1987 and approved on August 19, 1989. Some information was also contained in a [redacted]

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

In the original pharmacology review of NDA 19711, dated January 29, 1988, teratology studies in rats and mice were recommended as the requirements for approval.

In the amendment to pending NDA 19711 dated September 16, 1988, the sponsor submitted a **teratology study in rats (Report #3199.1)**. This study was reviewed on November 22, 1988. The results of the study showed that the combination drug products (100 mg ibuprofen / 15 mg pseudoephedrine) was not teratogenic in rats at doses up to 115 mg/kg.

The **teratology study in mice (Report #3199.2)** was submitted on March 1, 1996 as a fulfillment of Phase IV commitment. This study has not been reviewed. The review of the mice teratology study follows:

An oral teratology study in mice with WH-441-22 (Report #3199.2)

(WH-441-22 is a mixture of ibuprofen and pseudoephedrine HCl at a 100:15 w/w ratio.)

Study No. 3199.2, Vol. 26.1, page 00-0001--00-0449

[redacted]

Date of study initiation: April 1992
Date op study completion: February 11, 1993
GLP compliance: yes
QA reports: yes () no ()
Drug: Ibuprofen Lot #LFI-81, Pseudoephedrine HCl Lot #25690
Formulation/vehicle:
(Ibuprofen: Pseudoephedrine HCl=100:15 w/w ratio) in 1% aqueous methylcellulose.
Methods:
Crl:CD-1 (ICR) BR mice, 28 females/group.
Dose: Combination: 0, 11.5, 34.5, and 138 mg/kg/day (group. 1, 2, 3, and 4).
Ibuprofen only: 120 mg/kg/day (group 5).
Pseudoephedrine HCl only: 18 mg/kg/day (group 6).
Administered in volume of 10 ml/kg by gavage from gestation day 6 through 15.
Animals were euthanized on gestation day 18.

Results:
According to the sponsor, two animals died in 138 mg/kg/day group (group 4) were not treatment-related because no overt toxicity was observed in other animals of this group. One animal in group 5 (120 mg/kg/day ibuprofen) aborted on day 16 of gestation.

The pregnancy rate was 92.9 %, 96.4 %, 92.9 %, 92.9 %, 92.9 %, and 96.4 % for group 1-6, respectively.
Clinical signs in surviving animals were generally unremarkable. Two animals that died showed some signs including: dehydration, rough coat, decreased activity, labored breathing, and cool to touch, etc. The sponsor concluded that these effects were induced by experimental manipulation rather than drug effect because there was lack of toxicity in other study animals.
Body weight, body weight gain, and food consumption were comparable among animal groups.
Gross necropsy findings for surviving animals were generally unremarkable. Two dead animals in group 4 showed changes in GI tract, including reddened mucosa. The aborted animal in group 5 showed adhesion involving stomach and inferior surface of left lobe of liver.
Upon cesarean section, no difference among groups were found in the mean number of corpora lutea, implantation sites, viable fetuses, early and late resorptions, post-implantation loss, fetal sex ratios, and mean fetal body weights. There were no significant differences in fetal malformations or developmental variations among groups. The observed changes were those known to occur spontaneously in this strain of mice.

Summary of teratology study in mice:
In this teratology study in mice, no fetal external, visceral, or skeletal malformations or variations were observed at up to 138 mg/kg/day of the combination drug product (WH-441-22). In the maternal animals, only small toxicity, mostly in GI tract, was observed. There were no changes in the pregnancy parameters observed in the study. Similarly, no fetal toxicity and very little maternal toxicity were found in 120 mg/kg/day ibuprofen and 18 mg/kg/day pseudoephedrine HCl groups. It was concluded that WH-441-22 was not teratogenic in the mice study

Reproductive and developmental toxicology conclusion:
WH-441-22 was not teratogenic in the rat study at doses up to 115 mg/kg/day. At this high dose level the body weight gains was 28% lower than the control group from days 6 to 16 of gestation. No other obvious toxicity was observed in the rat study. The dose level of 115 mg/kg/day in the rat study was approximately 4 times of maximum adult human clinical dose (1380 mg/person/day or 27.6 mg/kg/day based on the 50 kg body weight). However, by converting the dose to HED (Human Equivalent Dose) using body surface area conversion, 115 mg/kg/day in rat is just about the human clinical dose (HED=115÷6=20 mg/kg/day).
In the mouse teratology study, WU-441-22 did not cause fetal malformation or variation at doses up to 138 mg/kg/day. The high dose in the mice study was approximately 5 times of maximum adult human clinical dose (138÷27.6=5). However, this dose level is below the clinical dose based on the body surface area conversion (HED=138÷12=11.5 mg/kg/day). Minor GI toxicity was observed in maternal animals at this high dose level. It was felt that the dose levels in the

rodent teratology study could have been set higher in order to have a larger margin of safety.

Labeling recommendation:
WH-441-22 is an OTC product. The labeling of this product will not have the Reproduction Section. There is no need to include the negative results from the teratology studies in the labeling.

VIII. SPECIAL TOXICOLOOGY STUDY:

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:
Conclusions: The fixed combination of the two active ingredients of this drug product, ibuprofen and pseudoephedrine HCl in 100:15 w/w ratio, has been marketed as an OTC product (NDA 19771) since 1989. The inactive ingredients of Children's CoAdvil Cold Suspension (NDA 21373) are all compendial products. There is no efficacy/ safety concern from the nonclinical point of view.
Recommendation: Approval of NDA 21373
Labeling with basis for findings: None.

Reviewer signature: _____
Conrad H. Chen, Ph.D.

Supervisor signature: Concurrence- _____
Josie Yang, Ph.D.

Non-Concurrence-

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

/s/

Conrad Chen
3/15/02 01:41:05 PM
PHARMACOLOGIST
The approval of NDA 21373 is recommended.
You have signed the hard copy already.

Josie Yang
3/15/02 02:04:35 PM
PHARMACOLOGIST

Div File

Review and Evaluation of Pharmacology and Toxicology Data

MAR 14 2000

Reviewer Name: Conrad H. Chen, Ph.D.
HFD-550

Drug Name: [redacted] (Ibuprofen Pseudoephedrine 15 mg per 5 mL)
Sponsor: Whitehall-Robins Healthcare
Date of Submission: March 2, 2000
Date of Receipt by Reviewer: March 7, 2000
Date of Review Completion: March 14, 2000
Information to Sponsor: Yes ( ) No (x)
Drug Category: NSAID/ Sympathomimetic Amine (Nasal Decongestant)
Proposed Indication: Temporary relief of symptoms associate with the common cold, sinusitis, and flu, including nasal congestion, head ache, body aches, pain, and fever, in children 2 years to <12 years old.
Related to: [redacted] and NDA 19771 (Advil Cold and Sinus Tablets/Caplets, Ibuprofen 200 mg/ Pseudoephedrine 30 mg)
Qualitative/ Quantitative Composition:

Ingredient	Mg/Dosage Unit
Ibuprofen USP	
Pseudoephedrine HCl USP	15
Xanthan Gum	
Microcrystalline Cellulose	
Carboxymethylcellulose Sodium	
Polysorbate 80 NF	
Glycerin	
Sorbitol Solution	
Sucrose	
Sodium Benzoate NF	
Disodium Edetate USP	
Citric Acid Hydrous USP	
Grape Flavor	
FD&C Red #40	
FD&C Blue #1	5
Purified Water	qs 5 mL

Proposed Clinical Study:

The following clinical studies will be conducted:

1. A single-dose, three-way crossover, pharmacokinetic study in 6 to <12 year old children. Thirty healthy children will be administered 220 mg ibuprofen/ 30 mg pseudoephedrine, 30 mg pseudoephedrine, or 200 mg ibuprofen with 5 to 14 days

wash-off periods. Blood samples will be taken via an indwelling catheter for pharmacokinetic study.

2. A single-dose, parallel group, confirmatory pharmacokinetic study in children ages 2 to <6 years. Approximately 50 children with symptoms of an acute upper respiratory tract infection will be enrolled. They will receive either 110 mg ibuprofen/ 15 mg pseudoephedrine or 15 mg pseudoephedrine in a parallel design. Blood samples for pharmacokinetic analysis will be drawn.
3. Multiple-use safety study in children 2 to <12 years old. Approximately 100 subjects with symptoms associated with common cold, sinusitis or flu will be enrolled. They will receive 110 mg ibuprofen/ 15 mg pseudoephedrine (for ages 2-5) or 220 mg ibuprofen/ 30 mg pseudoephedrine (for ages 6-11) every 6 hours, up to four times a day not exceeding 7 days for a cold or 3 days for a fever. The parent/ guardian will record each occurrence of an adverse experience during the course of the study. Vital signs will be recorded at screening, after 2-days dosing and at end of study.

The followings are the doses of Advil Cold & Sinus Suspension by age and body weight.

Age (yr.)	Weight Kg (lbs)	Ibuprofen (mg)	Dose Ibuprofen (mg/kg)	Dose Pseudoephedrine (mg)	Number of Teaspoon
11	33-43 (72-95)	220	5.1-6.7	30	2.0
9-10	27-32 (60-71)	220	6.8-8.1	30	2.0
6-8	22-27 (48-59)	220	8.2-10.1	30	2.0
4-5	16-21 (36-47)	110	5.1-6.7	15	1.0
2-3	11-16 (25-35)	110	6.9-9.7	15	1.0

1 teaspoon = Ibuprofen 110 mg and pseudoephedrine 15 mg

Preclinical Study:

Reference is made to NDA 19771 (CoAdvil/ Advil Cold & Sinus Tablets and Caplets) for ibuprofen/ pseudoephedrine non-clinical data.

Evaluation and Comment:

The combination known as Advil Cold & Sinus Tablets/Caplets (NDA 19771 & IND ——— consists of ibuprofen 200 mg/ pseudoephedrine 30 mg is marketed for temporary relief of symptoms due to upper respiratory infections in consumers 12 years of age or older. The purpose of current IND is to develop ———
) for the temporary relief of symptoms associated with the common cold, sinusitis (i.e. viral rhinosinusitis), and flu, including nasal congestion, head ache, body aches, pain, and fever, in children 2 years to <12 years old.

The proposed clinical trials in this IND are: two pharmacokinetic studies in children 2 to <6 years old and 6 to <12 years old, and one safety study in children 2 to <12 years old. The purpose of these trials is to demonstrate the bioequivalence, lack of interaction

between ingredients, and similarity of the pharmacokinetic profiles across age ranges. The proposed doses in the studies are within the doses recommended for Advil Cold & Sinus Tablets/ Caplets in adults and children above 12 years of age.

The sponsor referred to NDA 19771 for the non-clinical information. No new animal study has been submitted in the IND.

Recommendation:

There is no objection to the proposed clinical study by the reviewing pharmacologist.

/S/

Conrad H. Chen, Ph.D.
Pharmacologist

/S/
3-14-00

cc:
Div. file
/Original IND
HFD-550/Pharm/Chenco
HFD-550 TLPharm/Weir
HFD-550 MO/Fang
HFD-550Chem/Ho
HFD-550 CSO/Cook