CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-441

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-441
Review number: 001
Sequence number/date/type of submission: 000/February 28, 2002/Original NDA
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940-0871
Manufacturer for drug substance: Wyeth-Ayerst Laboratories, Rouses Point, NY
Reviewer name: Maria I. Rivera
Division name: Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD #: 550
Review completion date: October 17, 2002

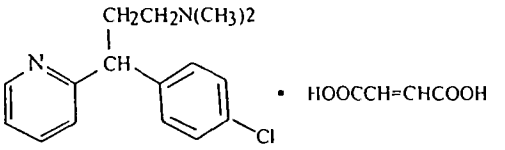
Drug:

Trade name: Advil® Allergy Sinus Caplets

Components

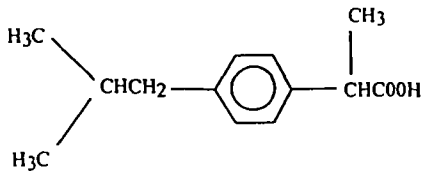
Chlorpheniramine maleate

Class: Antihistamine
Chemical name: 2-pyridinepropamine, 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:



Ibuprofen

Class: NSAID
Chemical name: (R,S)-2-(4-isobutylphenyl)-propionic acid
CAS registry number: 15687-27-1
Molecular formula/molecular weight: $C_{13}H_{18}O_2$/206.27
Manufacturer:



Pseudoephedrine HCl

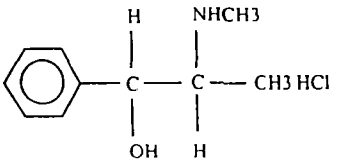
Class: Sympathomimetic

Chemical name: 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]



Relevant INDs/NDAs/DMFs:

NDA 18-989	Advil®
NDA 19-771	Advil® Cold & Sinus Tablets/Caplets
IND 61,725	Advil Multisymptom Allergy Sinus (Advil MSAS)
DMF [redacted]	Chlorpheniramine maleate
DMF [redacted]	Ibuprofen
DMF [redacted]	Pseudoephedrine HCl

Drug class: Analgesic/Decongestant/Antihistamine

Indication: [redacted] runny nose, sneezing, itching of nose or throat, itchy, watery eyes, headache, minor aches and pains, nasal congestion, and sinus [redacted] pressure in adults and children 12 years of age and older.

Clinical formulation:

Active Ingredients	mg/caplet
Ibuprofen USP	200
Pseudoephedrine HCl USP	30.0
Chlorpheniramine Maleate USP	2.00
Inactive Ingredients	
Silicon Dioxide Colloidal NF	
Silicon Dioxide NF	
Croscarmellose Sodium NF	
Glyceryl Behenate NF	
Hypromellose USP	
Microcrystalline Cellulose NF	
Microcrystalline Cellulose NF	
Starch, Pregelatinized NF	
Water Purified USP [A]	
Carnauba Wax NF	
Total Weight	

[A]Essentially removed during processing.

[B]Qualitative composition of is listed below

Hydroxypropyl Methylcellulose
Hydroxypropyl Methylcellulose
Titanium Dioxide
Hydroxypropyl Methylcellulose
FD&C Yellow No. 6/
Polyethylene Glycol
FD&C Red No. 40/.
FD&C Yellow No. 6/
Carnauba Wax

[C]Qualitative composition of is listed below (components marked * are essentially removed during processing):

Purified Water *
Iron Oxide Black

Propylene Glycol
Hydroxypropyl Methylcellulose

Route of administration: Oral

Proposed use: One caplet every 4-6 hours while symptoms occur and not to take more than 6 caplets in any 24-hour period, unless directed by a doctor. Maximum recommended daily dosing for individual ingredients would be 1200 mg ibuprofen, 180 mg pseudoephedrine, and 12 mg chlorpheniramine.

Disclaimer: Some text material is from Sponsor's submission.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approval of Advil® Allergy Sinus Caplets is recommended.

B. Recommendation for Nonclinical Studies

No studies are recommended.

C. Recommendations on Labeling

The product label does not contain any Pharm/Tox data to be reviewed.

II. Summary of Nonclinical Findings

A. 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) combination. 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 has been available OTC from Whitehall-Robins Healthcare since 1989 (Advil® Cold & Sinus Tablets/Caplets, NDA 19-771). The double combination product has the same content of ibuprofen/pseudoephedrine hydrochloride and the same dosing instructions as those proposed for 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. Therefore, the concern with the current NDA was to evaluate the potential for interaction effects when a third active ingredient (chlorpheniramine) was added to the combination. This was evaluated in clinical trial AD-99-01 (Electronic Submission Vol. # 27). 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 Multi-Symptom 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. Given that the clinical PK data showed no drug-drug interactions and that the safety profile of each active ingredient is well established, preclinical studies to address the safety of the triple combination are not considered necessary.

The teratogenic potential of the ibuprofen/pseudoephedrine hydrochloride combination was examined as part of the development program for Advil® Cold & Sinus Tablets/Caplets (NDA 19-771). The double combination was not teratogenic to rats or mice but the maximum doses used were similar or ~2-fold lower than the maximum clinical daily dose (when corrected for surface area),

respectively. Therefore, an adequate margin of safety was not achieved. Chlorpheniramine maleate is classified as Pregnancy Category B and is not expected to pose a teratogenic risk when added to the combination. No additional nonclinical studies were deemed necessary because ibuprofen is classified as Category B/D (third trimester) and pseudoephedrine hydrochloride is classified as Category C, and precautions already exists for the usage of each individual active ingredient during pregnancy.[1]

B. 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.

C. Nonclinical Safety Issues Relevant to Clinical Use

The pharmacology and toxicology of ibuprofen, pseudoephedrine hydrochloride, and chlorpheniramine maleate are well established. Clinicians are aware of the side effects they should monitor and precautions they should take.

III. Administrative

A. Reviewer signature: /S/
Maria I. Rivera, Ph.D.

B. Supervisor signature (Josie Yang, Ph.D.): Concurrence - /S/

Non-Concurrence - _____
(see memo attached)

C. cc: list:

NDA 21-441/Original NDA
HFD-550/Division File
/Pharm/Tox TL/JosieYang
/MO/Christina Fang
/PM/Jane Dean

[1] All Pregnancy Categories were obtained from Micromedex Integrated Index. DrugDex® Drug Evaluations.

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

No pharmacology studies were submitted with the proposed 200 mg ibuprofen/30 mg pseudoephedrine HCl/2 mg chlorpheniramine maleate combination product. All three active ingredients have been extensively studied and the pharmacologic properties of the drugs are well known. The Sponsor submitted the following information.

Ibuprofen, a propionic acid derivative, is an NSAID with analgesic and antipyretic properties that has been available OTC since 1984. Currently, the indications for this product include relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, and backache, for the minor pain of arthritis, for the pain of menstrual cramps, and for the reduction of fever. The mode of action appears to be the inhibition of prostaglandin synthesis, specifically, the cyclo-oxygenase enzymes COX1 and COX2. The currently approved dosing instructions for OTC ibuprofen are 1-2 tablets (200-400 mg) every 4-6 hours, up to 1200 mg per day (no more than 10 days for pain, 3 days for fever).

Pseudoephedrine is an orally active indirect-acting sympathomimetic amine, which stimulates adrenergic nerve endings to release norepinephrine. The released norepinephrine acts at vascular α_1-receptors in the upper respiratory tract (where its action is more specific) to cause vasoconstriction of nasal and sinus vessels and decongestion of swollen nasal mucosal tissues. Pseudoephedrine is recognized as an effective agent for the temporary relief of nasal congestion due to the common cold, hay fever, other allergies, or sinusitis. The drug is listed in the Final Monograph of Nasal Decongestants (59 FR 43386; August 23, 1994) as safe and effective (Category I), and is indicated for use in adults and children 2 years or older (for adults and children 12 years and older up to 240 mg in 24 hours). It is currently available in numerous OTC products. In 1989, the combination of pseudoephedrine 30 mg and ibuprofen 200 mg was approved for OTC use as an analgesic/decongestant (Advil® Cold & Sinus Tablets/Caplets, NDA 19-771). The recommended dosage for adults is one tablet every 4 to 6 hours while symptoms persist. If symptoms do not respond to one tablet, two tablets may be used, but no more than six tablets should be taken in 24 hours.

Chlorpheniramine, a classical H_1-receptor antagonist (antihistamine), has been available for more than 40 years as a nonprescription medication for relief of allergic rhinitis symptoms. It has been shown to be effective against major histamine-mediated symptoms, i.e., sneezing, itching and rhinorrhea. It is considered a Category I antihistamine according to the Final Monograph for OTC Antihistamines (21 CFR 341.12). The recommended dose of chlorpheniramine for adults is 4 mg every 4 to 6 hours while symptoms persist, up to 24 mg per 24 hours.

II. SAFETY PHARMACOLOGY:

No safety pharmacology studies were submitted with the combination. 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 and ibuprofen or chlorpheniramine maleate are currently marketed as OTC products for use in adults and children.

III. PHARMACOKINETICS/TOXICOKINETICS:

No PK/TK studies were submitted with the combination. The PK profile of ibuprofen, pseudoephedrine hydrochloride, and chlorpheniramine maleate have been well characterized in humans. In this NDA, clinical trials were conducted to determine potential drug-drug interactions when the active ingredients are given as a combination product (Refer to Biopharmaceutics review).

III. GENERAL TOXICOLOGY:

No nonclinical studies were conducted with the triple combination. The Sponsor made reference to NDA 18-989 (Advil®) for extensive nonclinical data supporting safe use of ibuprofen OTC with doses up to 1200 mg/day for adults. The Sponsor also referred to NDA 19-771 (Advil® Cold & Sinus Tablets/Caplets) for safety information supporting safe OTC use of an ibuprofen/pseudoephedrine (200 mg/30 mg) combination product with adult daily doses up to 1200 mg ibuprofen and 180 mg pseudoephedrine.

The following information was submitted by the Sponsor regarding the safe use of pseudoephedrine hydrochloride and chlorpheniramine maleate. Pseudoephedrine hydrochloride is Generally Recognized As Safe and Effective (GRASE) for OTC use individually or as a combination oral nasal decongestant ingredient with doses up to 240 mg/day for adults and children over 12 years (21 CFR 341.80(d)(1)(ii)). Chlorpheniramine maleate is GRASE for OTC use as an individual or combination antihistamine ingredient with doses up to 24 mg/day for adults and children over 12 years (21 CFR 341.72(d)(3)). Category I combinations of Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic ingredients include simultaneous use of Category I single ingredients: oral nasal decongestants including pseudoephedrine, internal analgesic/antipyretics including aspirin and acetaminophen, and oral antihistamines including chlorpheniramine.

The Sponsor conducted an evaluation of the literature published from 1966 through October 2001 for the individual ingredients as well as the proposed combination. The search consisted of Medline, Embase, Biosis, Toxline, Derwent Drug File, and SciSearch. The Sponsor stated that no information was found to suggest a safety concern for the usage of the individual active ingredients or the proposed combination.

During the IND phase of the current NDA (IND 61,725), Whyeth Consumer Healthcare (previously named Whitehall-Robins Healthcare) provided a literature review of the nonclinical studies conducted for ibuprofen, pseudoephedrine hydrochloride, and chlorpheniramine maleate, and provided summaries of the nonclinical studies conducted for the combination of ibuprofen and pseudoephedrine hydrochloride. The following summary was taken from the Pharm/Tox review of IND 61,725 (Jan. 26, 2001, by Maria I. Rivera) with some modifications.

The nonclinical studies summarized for ibuprofen included acute, subchronic, and chronic toxicity studies in mice, rats, dogs, and baboons. Gastric ulcers and/or erosions were side effects common to all species. Nephrotoxicity (papillary necrosis/hyalinization) was observed in baboons and rats. Other side effects were sedation (acute studies), depressed growth, anemia, anorexia, and CNS depression (subchronic studies).

Regarding pseudoephedrine hydrochloride and chlorpheniramine, limited nonclinical data was presented. The studies cited for pseudoephedrine hydrochloride consisted of the LD_{50} values and the toxic effects found in several species (i.v. dose in mice: increase motor activity, piloerection, mydriasis, and death from respiratory exhaustion; oral doses in various species: increased respiratory activity, salivation, lacrimation, loss of pupilary reflex reaction to light, tremor, convulsions and cardiac arrhythmias). The approximate oral LD_{50} values were 726 mg/kg (mouse), 2206 mg/kg (rat), 1117 mg/kg (rabbit), 105 mg/kg (beagle dog), and 307 mg/kg (mongrel dog). In the case of chlorpheniramine, the Sponsor cited oral subchronic studies done in the rat (6 weeks) and monkey (7 weeks) that did not reveal any abnormalities. No data was presented but it was mentioned that the toxicity produced in the species tested was typical to that observed for most antihistamines. The general pattern of CNS stimulation was characterized by signs of irritability at lower doses, and tremors, mydriasis, and convulsions at higher doses.

The combination of ibuprofen and pseudoephedrine hydrochloride is an OTC product marketed by Whitehall Robins since 1989 (Advil® Cold and Sinus, NDA 19-771). As part of the studies requested by FDA before the approval of this drug, the Sponsor found the combination of ibuprofen and pseudoephedrine hydrochloride had a relatively low order of toxicity after oral administration in mice and rats (Refer to table below).

Combination Ibuprofen/Pseudoephedrine	LD_{50} (Range)	
	Rats (g/kg)	Mice (g/kg)
200 mg/30 mg	1.45 (1.38-1.54)	2.40 (1.69-3.41)
200 mg/60 mg	1.40 (1.26-1.55)	1.19 (0.42- 2.92)
300 mg/60 mg	0.85 (0.68-1.06)	1.78 (1.27-2.49)

IV. GENETIC TOXICOLOGY:

No nonclinical studies were conducted with the triple combination. The table below contains information provided by the Sponsor under IND 61,725 or found in the literature for ibuprofen and chlorpheniramine. No genotoxicity studies were found for pseudoephedrine in Pubmed, Embase, and Toxnet literature databases.

SUMMARY OF GENOTOXICITY STUDIES FOR IBUPROFEN AND CHLORPHENIRAMINE

DRUG/ASSAY	DESCRIPTION	DOSES	RESULTS
Ibuprofen[1]			
Ames test	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537,or TA 1538, ± metabolic activation (S9)	1-1000 µg/ml	Negative
	Salmonella typhimurium TA97A, TA 100, ± metabolic activation (S9)	1-5000 µg/ml	Negative
Chlorpheniramine maleate[1,2]			
Ames test	*Salmonella typhimurium* TA98, TA100, TA 1535, or TA 1537, ± metabolic activation (S9)	333-3333 µg/plate or 100-10000 µg/plate	Negative
Mouse lymphoma cells	L5178Y (TK+/TK-) strain; – metabolic activation (S9)	90-230 µg/ml	Negative
Mouse lymphoma cells	L5178Y (TK+/TK-) strain; - metabolic activation (S9)	10-250 µg/ml	Negative
Chromosome aberrations	Chinese hamster ovary cells, ± metabolic activation (S9)	Not specified	Positive at the highest dose in the absence of S9
Sister-chromatid exchange	± metabolic activation (S9)	Not specified	Weak but reproducible ↑ in sister-chromatid exchanges in the absence of S9

[1]Toxnet Database [2]National Toxicology Program (NTP), Toxicology and Carcinogenesis Studies of Chlorpheniramine Maleate (CAS No 113-92-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). TR-317. http://ntp-server.niehs.nih.gov/

Labeling recommendations: None

VI. CARCINOGENICITY:

No nonclinical studies were conducted with the triple combination. The table below contains information provided by the Sponsor under IND 61,725 or found in the literature for ibuprofen and chlorpheniramine. No carcinogenicity studies were found for pseudoephedrine in Pubmed, Embase, and Toxnet literature databases.

SUMMARY OF TWO-YEAR CARCINOGENICITY STUDIES FOR IBUPROFEN AND CHLORPHENIRAMINE

DRUG/SPECIES	DOSES (MG/KG/DAY)		RESULTS
	MALES	FEMALES	
Ibuprofen			
— Wistar Rats[1]	0, 180 in the diet; ↓ to 60 at week 56	0, 180 in the diet; ↓ to 60 at week 56	Negative
— Wistar Rats[2]	0, 20, 60, 120 in the diet	0, 20, 60, 120 in the diet	Negative
— Mice[3]	0, 300 in the diet; ↓ to 100 at week 46	0, 300 in the diet, ↓ to 100 at week 46	Negative
Chlorpheniramine maleate[4]			
Fisher 344 Rats[5]	0, 15, 30 (gavage)	0, 30, 60 (gavage)	Negative
B6C3F1 Mice[5]	0, 25, 50 (gavage)	0, 100, 200 (gavage)	Neoplastic lesions: Negative Non-neoplastic lesions In females, there was an ↑ incidence of thyroid follicular cell cysts (2/48, 10/49, 13/47), thyroid gland follicular cell hyperplasia (3/48, 29/49, 36/47), and thyroid gland follicular cell adenomas (0/48, 4/49, 2/47)

[1]n = 30 animals/sex/dose, [2]n = 40 animals/sex/dose; [3]n=50 animals/sex/dose, study duration was 80 weeks; [4]National Toxicology Program. Toxicology and Carcinogenesis Studies of Chlorpheniramine Maleate (CAS No 113-92-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies), TR-317, http://ntp-server.niehs.nih.gov/, [5]n=50 animals/sex/dose

Labeling recommendations: None

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

No reproductive toxicity studies were submitted with the combination. The Sponsor referred to two studies, previously submitted, in which the combination of ibuprofen and pseudoephedrine was evaluated for its teratogenic potential. These studies were reviewed by Conrad Chen, Ph.D, and a summary of the reviews is given below.

The initial study, "Teratology Study in Rats with WH-441-22" was submitted on September 19, 1988 with NDA 19-771, CoAdvil®, later changed to Advil®Cold & Sinus (200 mg ibuprofen/30 mg pseudoephedrine). No developmental toxicity was found in rats given ibuprofen/pseudoephedrine at doses up to 115 mg/kg/day (100/15 mg/kg/day), ibuprofen alone at a dose of 100 mg/kg/day, and pseudoephedrine alone at a dose of 15 mg/kg/day (see Appendix). At the combination high dose, dams showed a 28% decrease in body weight gain from days 6 to 16 of gestation (Data from Dr. Conrad Chen review for NDA 21-373, see below). The human equivalent dose (HED) for the high dose = 18.5 mg/kg. This dose is 0.8-fold the maximum daily clinical dose of the combination (23 mg/kg, 60 kg person). The reviewer concluded that doses higher than 115 mg/kg/day should have been used.

The second study, "An Oral Teratology Study in Mice with WH-441-22" was submitted on March 1, 1996, as a post-approval commitment for NDA 19-771. This study was reviewed under NDA 21-373 (Children's Advil Cold Suspension, review completion date 2/8/2002). No

developmental toxicity was found in mice given ibuprofen/pseudoephedrine at doses up to 138 mg/kg/day (120/18 mg/kg/day), ibuprofen alone at a dose of 120 mg/kg/day, and pseudoephedrine alone at a dose of 18 mg/kg/day. Minor GI toxicity was observed in the dams treated with the combination high dose. The HED for the high dose = 11.2 mg/kg, which is ~2-fold lower than the maximum clinical daily dose (23 mg/kg, 60 kg person). Similar to the conclusion reached in the rat reproductive toxicity study, the reviewer felt that higher doses should have been used in order to have a larger margin of safety.

Labeling recommendations: None

VIII. SPECIAL TOXICOLOGY STUDIES:

No special toxicology studies were submitted.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: The Sponsor did not conduct any nonclinical studies in this NDA. The studies presented were obtained from literature sources or conducted by the Sponsor as part of the development program for NDA 19-771 (Advil®Cold & Sinus). The safety profile and the efficacy of each of the individual active ingredients as well as that of combination products containing pseudoephedrine hydrochloride plus ibuprofen or chlorpheniramine maleate have been well established through extensive clinical evaluation and post-marketing experience. The combination of ibuprofen and pseudoephedrine hydrochloride has been available as an OTC product from Whitehall-Robins Healthcare since 1989 (NDA 19-771). This combination exists as a tablet/caplet form containing the same concentration (200 mg ibuprofen/30 mg pseudoephedrine) and dosing instructions as those proposed for Advil® Allergy Sinus Caplets.

Although the absence of a pharmacokinetic interaction between ibuprofen and pseudoephedrine was established during the approval process for NDA 19-771, the concern with the current NDA was to evaluate the potential for interaction effects when a third active ingredient (chlorpheniramine) was added to the combination. This was evaluated in clinical trial AD-99-01. 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. Adverse effects were observed in 20% of the patients and included asthenia, anorexia, nausea, dizziness, and somnolence. Most adverse effects were mild in intensity and there were no reports of severe adverse effects. Therefore, no pre-clinical studies were deemed necessary.

The combination of ibuprofen/pseudoephedrine hydrochloride (NDA 19-771) was not teratogenic to rats or mice. The maximum doses used in the rat and mouse study were similar or ~2-fold lower than the maximum clinical daily dose (when corrected for surface area), respectively. Therefore, an adequate margin of safety was not achieved. Chlorpheniramine maleate is classified as Pregnancy Category B and is not expected to pose a teratogenic risk when added to the combination. No additional preclinical studies were deemed necessary because ibuprofen is classified as Category

B/D (third trimester) and pseudoephedrine hydrochloride is classified as Category C, and precautions already exists for the usage of each individual active ingredient during pregnancy.[1]

General Toxicology Issues: No toxicology issues.

Recommendations: The post-marketing experience with each individual component of the combination and with combination products containing pseudoephedrine hydrochloride plus ibuprofen or chlorpheniramine maleate supports that the doses in Advil® Allergy Sinus Caplets are safe. Approval of Advil® Allergy Sinus Caplets is recommended.

Labeling with basis for findings: The product label does not contain any Pharm/Tox data to be reviewed.

X. APPENDIX/ATTACHMENTS:

Addendum to review: Review of NDA 19-771

Other relevant materials (Studies not reviewed, appended consults, etc.): None

Any compliance issues: None

REVIEW AND EVALUATION OF PHARMACOLOGY
AND TOXICOLOGY DATA

Date of Submission: September 19, 1988
Date of Review: November 22, 1988

NDA 19-771

APPLICANT: Whitehall Laboratories
New York, New York 10010-4076

DRUG: CoAdvil (ibuprofen 200 mg/pseudoephedrine 30 mg)

CATEGORY: NSAID/adrenergic agonist (nasal decongestant)

BACKGROUND

NDA 19-771 was initially submitted on September 3, 1987. In the pharmacologist review (dated January 29, 1988) of this submission, it was recommended that the teratology studies in rats and in mice on the combination be conducted. Herein with the applicant submitted the final report of a study entitled "Teratology Study in Rats with WH-441-22" for our review.

PRECLINICAL STUDY

Teratology study in rats with WH-441-22.

WH-441-22 is a mixture of WH-2061 (ibuprofen) and WH-3224 (pseudoephedrine) at a 100:15 ratio.

Twenty-five pregnant Sprague-Dawley — CD female rats/group.

Dose: WH-441-22 (11.5, 34.5, and 115 mg/kg/day), WH-2061 (100 mg/kg/day), WH-3224 (15 mg/kg/day), and vehicle control groups.

The animals were treated from gestation day 6 through 15 by gavage. Since human clinical dose of CoAdvil is 1-2 tablets, 3 times a day, the maximum dose in 50 kg body weight person is 1200 mg/50 kg = 24 mg/kg ibuprofen and 180 mg/50 kg = 3.6 mg/kg pseudoephedrine. Therefore, the mid-dose in rat teratology study is in the range of clinical maximum dose and the high-dose in the study is about 4 times of the maximum clinical dose.

The dosage volume was 10 ml/kg for all study group. The dosage mixtures were prepared fresh daily in the 190 methylcellulose vehicle.

The study group, dose levels, and the treatment regimen are presented below:

Treatment Group	Dosage Material (mg/kg/day) WH-441-22*	WH-2061	WH-3224	Dosage Volume (ml/kg)	Number of Animals/ Group
1	0	0	0	10	25
2	11.5	10	1.5	10	25
3	34.5	30	4.5	10	25
4	115	100	15	10	25
5	0	100	0	10	25
6	0	0	15	10	25

*WH-441-22 is a mixture of WH-2061 and WH-3224 at a 100:15 ratio, respectively (weight to weight).

There was no treatment related death in the study. A few deaths were caused by the intubation error. Reduced body weight gains were noted during day 6-16 in group 4 (115 mg WH-441-22) and group 5 (100 mg WH-2061). Mean food intake was slightly but significantly reduced in the same groups stated above during the treatment. Enlarged mesenteric lymph nodes were observed in all groups including the control. The biological significance of this change was not known. Mean numbers of viable fetuses, early and late resorptions, corpora lutea and total implantation sites, as well as mean fetal weights were comparable between the control and the treated groups. The changes of sex ratio in some treated groups could be attributable to the skewed sex ratio of control group (to having more males) than is usually seen. The sponsor tried to substantiate this argument by presenting the sex ratio of historical control data (M:F = 2037:2040 = 0.999).

The incidence of fetal malformations was similar in the control and the treated groups. The observed malformations included anophthalmia, microphtalmia, omphalocele, edema, hydrocephaly, sternoschises, fused sternebre and vertebral anomaly.

EVALUATION AND COMMENT

In the current submission a teratology study in the rat with a fixed combination of ibuprofen/pseudosephedrine (100:15) was presented. It was reported that no treatment related fetal malformation were observed in the study.

The dosage levels chosen in the study were based upon a preliminary study using groups of virgin female rats. The high dose chosen, 115 mg/kg, was about 4 times of the maximum clinical dose of CoAdvil. The mid-dose chosen, 34.5 mg/kg, was about the maximum clinical dose of CoAdvil (1200 mg ibuprofen/180 mg pseudoephedrine per day). The change in body weight gain of the high dose pregnant group was statistically significant but was small. It was felt that the doses higher than 115 mg/kg CoAdvil (for example 138 mg/kg, 161 mg/kg, or 184 mg/kg) could probably be tolerated as well by animals. No reason for choosing 115 mg/kg as the high dose in teratology study was given in the Appendix A (Preliminary Study in Nonpregnant Rats with WH-441-22). The high dose chosen, 115 mg/kg, is about 4 times of maximum clinical dose.

It is recommended that a higher dose than which is minimally tolerable by the animals in the preliminary dose-range-finding study should be selected in the actual teratology study in the future.

In this submission, the applicant submitted a teratology study in rats. No teratological effect was observed at doses up to 115 mg/kg in rats. In pharmacologist review of NDA 19-771, dated January 29, 1988, two teratology studies were quoted as a requirement for the approval of this NDA. The applicant should be reminded to conduct a teratology study in a second specie of animal as recommended previously. In the study the dosage level should be raised to a maximally tolerable range in order to maximize the effect if there is any.

/S/ Dec. 27, 1988

Conrad H. Chen, Ph.D.

cc:
Original NDA 19-771
HFD-150/Division File
HFD-150/CHChen
HFD-151/CSO
HFD-102
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Wang 1075Y

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