CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-587

CHEMISTRY REVIEW(S)

NDA 21-587

Children's Advil Allergy Sinus/ [redacted]

Wyeth Consumer Healthcare

Bart Ho
HFD-550
HFD-560

Chemistry Review Data Sheet

1. NDA 21-587

2. REVIEW #: 2

3. REVIEW DATE: 2/10/04

4. REVIEWER: Bart Ho

5. PREVIOUS DOCUMENTS:

Submission	Document Date
Original	4-23-03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment 1	12-19-03
Amendment 2	1-14-04
Amendment 3	2-3-04
Amendment 4	2-12-04

7. NAME & ADDRESS OF APPLICANT:

Name: Whitehall-Robins

Address: Five Giralda Farms, Madison, NJ 07940-0871

Representative: David Smith Ph.D., Director, Regulatory Affairs

Telephone: 973-660-6806

8. DRUG PRODUCT NAME/CODE/TYPE:

a)Proprietary Name: Children's Advil Allergy Sinus/.

b)Non-Proprietary Name (USAN):

Ibuprofen/Pseudoephedrine HCl/Chlorpheniramine Maleate

c)Code Name/# (ONDC only):N/A

d)Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:
505(b)

10. PHARMACOL. CATEGORY: Symptoms of allergic rhinitis and the common cold.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY:

Ibuprofen, 100 mg/Pseudoephedrine HCl, 15 mg/Chlorpheniramine Maleate, 1 mg/5 mL

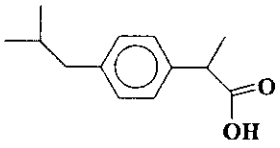
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___x___Not a SPOTS product

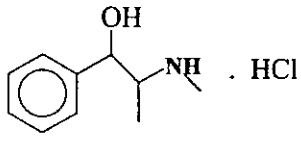
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Ibuprofen

206.28

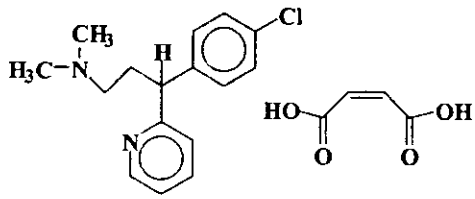
$C_{13}H_{18}O_2$



Pseudoephedrine HCl

201.69

$C_{10}H_{15}NO.HCl$



Chlorpheniramine Maleate

390.86

$C_{16}H_{19}CN_2.C_4H_4O_4$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See table below

DMF	Type	Holder	Item/Component	Review Date	Status
	II			2-13-03	3
	II			2-14-03	3
	II			2-14-03	3
	II			12-10-02	3
	V			10-20-03	1
	IV			10-20-03	1
	III			1/24/03	3
	III			5/29/02	3
	III			4/5/02	3
	III			5/29/02	3
	III		)	1/27/03	3
	III			5/31/02	3
	III			3/21/03	3
	III			1/24/03	3
	III			1/24/03	3
	III		ant	1/24/03	3
	III			1/24/03	3
	III			1/20/04	3

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

B. Other Documents: IND 63,999

18. STATUS: None

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biopharm	N/A		
EES	Found Acceptable		
Pharm/Tox	N/A		
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical Exclusion		
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-587

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval based on the chemistry point of view

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

Description of the Drug Product(s) and Drug Substance(s)

1) Drug Substances

Ibuprofen:

[redacted]

Pseudoephedrine HCl:

[redacted]

Chlorpheniramine Maleate:

[redacted]

2) Drug Product

The drug product, Children's Advil Allergy Sinus/ [redacted] (Ibuprofen/Pseudoephedrine HCl/Chlorpheniramine Maleate), is a suspension containing Ibuprofen, 100 mg, Pseudoephedrine HCl, 15 mg, and Chlorpheniramine Maleate, 1 mg/5 mL.

Ibuprofen/Pseudoephedrine HCl/Chlorpheniramine Maleate will be marketed in 1 oz, [redacted] and 8 oz [redacted] under the brand names Children's Advil® Allergy Sinus and [redacted]

There are basically no differences in the formulations proposed for marketing and the formulation on clinical trial with the exception of flavoring and color. Due to rapid dissolution of the drug product, particle sizes of ibuprofen, pseudoephedrine HCl and chlorpheniramine maleate drug substances are not considered an important factor.

b. Description of How the Drug Product is Intended to be Used

Ibuprofen/Pseudoephedrine HCl/Chlorpheniramine Maleate will be orally administered. Pseudoephedrine HCl is a decongestant. Chlorpheniramine maleate is an antihistamine, and ibuprofen is a pain reliever. Recommended doses for adults are two teaspoons every 6 hours not more than 4 times a day. The combination of ibuprofen, pseudoephedrine HCl and chlorpheniramine maleate is new and is intended for the relief of symptoms of allergic rhinitis and the common cold. Wyeth claims that the product is safe and non-habit-forming.

Satisfactory room temperature stability data (25°C/60% RH) of [redacted] on one clinical batch, 3 full scale NDA batches, Berry Flavors, and [redacted] are submitted in this amendment. [redacted] months expiration date for drug product stored in the proposed container/closure systems at room temperature (25°C/60% RH) was granted.

c. Basis for Approvability or Not-Approval Recommendation

Based on the chemistry point of view, NDA 21-587 is recommended for approval. Deficiencies sent to the firm have successfully been responded in the amendment.

In the current amendment, a lower limit [redacted] for unspecified impurities related to chlorpheniramine based on ICH threshold for identification was proposed. The proposed limit in the original submission based on ICH qualification was [redacted] A specification for total impurity [redacted] was also proposed.

Stability data indicated that the drug product was stable for the [redacted] period studied when stored in the proposed container/closure systems of [redacted] bottles (1 oz [redacted]) and [redacted] bottles (8 oz). Little or no degradation was found. Potencies varied; however, there was no evidence of a trend in decreasing in potency for the period studied. Twenty-four months expiration date, based on the stability data submitted in the amendment, was granted.

All stability samples almost achieved —— dissolution in 5 minutes for all the three APIs. The proposed dissolution criterion of not less than—— Q) in 10 minutes has been revised to —— Q) in 10 minutes per the request of BioPharm reviewer.

Currently proposed criteria for the known and unknown degradants from ibuprofen, pseudoephedrine HCl and chlorpheniramine maleate are based on ICH thresholds for Identification/Qualification. Esters of ibuprofen are rapidly dissociated in humans, therefore, they present no toxicity consequence.

Ibuprofen drug substance is manufactured by ——
—— Pseudoephedrine HCl is manufactured by ——
—— Chlorpheniramine is manufactured by ——
—— The drug product of a combination of Ibuprofen/Pseudoephedrine HCl/Chlorpheniramine Maleate, distributed commercially, will be manufactured, tested and packaged at Wyeth Pharmaceutical Co., 2248 Darbytown Road, Richmond, VA 23231. All the facilities specified in the application have been inspected and were found acceptable by the compliance.

III. Administrative

a. Reviewer's Signature N/A

Endorsement Block N/A

CC Block N/A

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ON ORIGINAL

9 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Bartholomew Ho
2/13/04 12:08:23 PM
CHEMIST

John Smith
2/13/04 12:47:27 PM
CHEMIST

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NDA 21-587

Children's Advil Allergy Sinus/ [redacted]

Wyeth Consumer Healthcare

Bart Ho
HFD-550
HFD-560

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-587

2. REVIEW #: 1

3. REVIEW DATE: 02/13/04

4. REVIEWER: Bart Ho

5. PREVIOUS DOCUMENTS: N/A

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Submission(s) Reviewed	Document Date
Original	4-23-03

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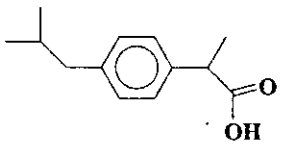

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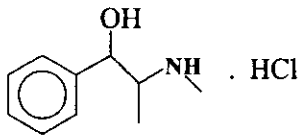

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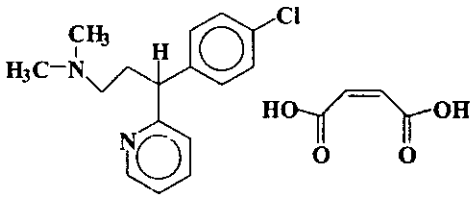

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	III			5/31/02	3
	III			3/21/03	3
	III			1/24/03	3
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	III	K		1/24/03	3
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B. Other Documents: IND 63,999

18. STATUS: None

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
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EES	To be inspected		
Pharm/Tox	N/A		
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical Exclusion		
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-587

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the chemistry point of view, NDA 21-587 is approvable pending the results of the inspection of the facilities is listed in the NDA. Comments should be forwarded to the sponsor for response.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

a. Description of the Drug Product(s) and Drug Substance(s)

1) Drug Substances

Ibuprofen:

[redacted]

Pseudoephedrine HCl:

[redacted]

Chlorpheniramine Maleate:

[redacted]

Esters of ibuprofen are rapidly dissociated in humans, therefore, present no toxicity consequence.

[redacted]

Ibuprofen/Pseudoephedrine HCl/Chlorpheniramine Maleate, is manufactured, tested and packaged at Wyeth Pharmaceutical Co., 2248 Darbytown Road, Richmond, VA 23231. All the facilities specified in the application have been scheduled to be inspected.

NDA 21-587 currently is deficient. Data to support the claim that antimicrobial activity remains effective when sodium benzoate contained in the drug product is at [redacted] of the initial concentration has not been submitted. Not testing unspecified degradants and microbial limits at drug product release is not acceptable. DMF [redacted] should be updated to provide information on the [redacted] that will be used for the manufacture of the dosing cup. The limit for unspecified individual degradants related to chlorpheniramine should be established based on ICH threshold for identification. The limit of total unspecified degradants should also be revised. Accuracy of the amount delivered by using the proposed dosing cup should be validated. Reduced stability testing proposed at second, third year and each year thereafter is not acceptable at this time. The amount of stability data submitted would not support [redacted] expiration date firm requested.

III. Administrative

a. Reviewer's Signature N/A

b. Endorsement Block N/A

c. CC Block N/A

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Bartholomew Ho
2/13/04 12:16:44 PM
CHEMIST

John Smith
2/13/04 12:43:38 PM
CHEMIST

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21587/000
Org Code: 550
Priority: 3S
Stamp Date: 24-APR-2003
PDUFA Date: 24-FEB-2004
Action Goal:
District Goal: 26-DEC-2003

Sponsor: WYETH CONS
5 GIRALDA FARMS
MADISON, NJ 079400871
Brand Name: CHILDRENS ADVIL ALLERGY SINUS/ [redacted]
Estab. Name:
Generic Name: IBUPROFEN/PSEUDOEPHEDRINE HCL/CHLORPHENI
Dosage Form: (SUSPENSION)
Strength: 100/15/1 MG PER 5 ML

FDA Contacts: B. HO Review Chemist (HFD-550) 301-827-2050
J. SMITH Team Leader (HFD-550) 301-827-2529

Overall Recommendation: ACCEPTABLE on 24-NOV-2003
by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment: [redacted]

DMF No:
Responsibilities:
Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-NOV-03
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: [redacted]

DMF No: AADA:
Responsibilities:
Profile: [redacted] OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-NOV-03
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-NOV-03
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

SUMMARY REPORT
ESTABLISHMENT EVALUATION REQUEST

Establishment:	CFN: 1120199 FEI : 1120199 WYETH AYERST LABORATORIES 2248-2258 DARBYTOWN RD RICHMOND, VA 23231
DMF No:	AADA:
Responsibilities:	FINISHED DOSAGE MANUFACTURER
Profile:	LIQ OAI Status: NONE
Last Milestone:	OC RECOMMENDATION
Milestone Date:	19-NOV-03
Decision:	ACCEPTABLE
Reason:	DISTRICT RECOMMENDATION

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ON ORIGINAL