CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-441

CHEMISTRY REVIEW(S)

NDA 21-441

Advil® Allergy Sinus Caplets

Whitehall Robins

Vispi P. Bhavnagri
HFD 550

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-441

2. REVIEW #: 1

3. REVIEW DATE: 10-Dec-2002

4. REVIEWER: Vispi P. Bhavnagri

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-Feb-2002
Minor Chem. Amendment (BC)	26-Aug-2002
Minor Chem. Amendment (BC)	16-Sep-2002
Minor Chem. Amendment (BC)	15-Nov-2002
Minor Chem. Amendment (BC)	03-Dec-2002
Minor Chem. Amendment #1 (BC)	10-Dec-2002
Minor Chem. Amendment #2 (BC)	10-Dec-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Whitehall-Robins
Address:	5, Giraldia Farms, Madison, NJ 07940-0871
Representative:	Mary H. Davis, Director, Regulatory Affairs
Telephone:	973-660-5825

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Advil® Allergy Sinus Caplets
b) Non-Proprietary Name (USAN): Ibuprofen/pseudoephedrine hydrochloride/ 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: 505B

10. PHARMACOL. CATEGORY: Pain reliever/nasal decongestant /antihistamine

11. DOSAGE FORM: Caplets

12. STRENGTH/POTENCY: Ibuprofen/pseudoephedrine hydrochloride/ chlorpheniramine maleate (200 mg/30 mg/2 mg)

13. ROUTE OF ADMINISTRATION: Oral

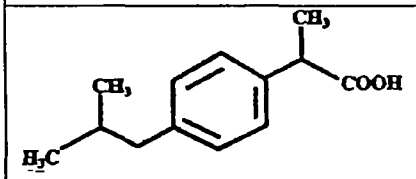
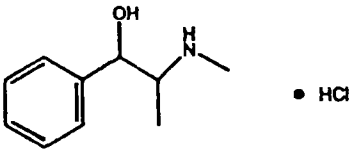
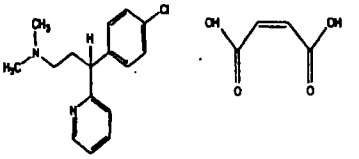
14. Rx/OTC DISPENSED: ___Rx __X__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) [Note24]:

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Ibuprofen	**Pseudoephedrine Hydrochloride**	**Chlorpheniramine Maleate**
		
(±)-2-(p-Isobutylppenyl) propionic acid or **(R,S)-2-(4-Isobutylphenyl) propionic acid**	(+)-∝ -[1-(methylamino)ethyl] benzenemethanol hydrochloride	2-Pyridinepropanamine, gamma -(4-chlorophenyl)-N, N-dimethyl-, (Z)-2-butenedioate (1:1).
$C_{13}H_{18}O_2$	$C_{10}H_{15}NO.HCl$	$C_{16}H_{19}CN_2 \cdot C_4H_4O_4$
206.29	201.69	390.86

17. RELATED/SUPPORTING DOCUMENTS:

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Ibuprofen DS	3	Adequate	10/30/96	
	II		Pseudoephedrine Hydrochloride	3	Adequate	9/13/01	
	II		Chlorphenir-amine Maleate	1	Adequate	12/4/02	
	III			4	N/A		
	III			1	Adequate	12/5/02	
	III			1	Adequate	12/5/02	

[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")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61,725	
NDA	19-771	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	7/16/02	J. Ambrogio
Pharm/Tox	Approval	10/17/02	M. Rivera
Biopharm	Acceptable	10/7/02	T. Ghosh
LNC	N/A		
Methods Validation	Will be sent to FDA Labs		
OPDRA	N/A		
EA	Categorical Exclusion		
Microbiology	N/A		

The Chemistry Review for NDA 21-441

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved from a CMC standpoint.

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

None

II. Summary of Chemistry Assessments

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

Drug Substances:

Ibuprofen:

Ibuprofen is manufactured and supplied by ——————————————— The manufacture and control of the drug substance were referenced to DMF —— The DMF has been recently reviewed and found to be adequate. Test and acceptance criteria meet the requirements of the USP.

Pseudoephedrine Hydrochloride:

Pseudoephedrine hydrochloride is manufactured and supplied ——————————————— . The manufacture and control of the drug substance were referenced to DMF —— The DMF has been recently reviewed and found to be adequate. Test and acceptance criteria meet the requirements of the USP.

Chlorpheniramine Maleate

Chlorpheniramine maleate is manufactured by ——————————————— in accordance with their drug master file (DMF —— . The DMF was last reviewed by Dr. Vibhakar Shah of HFD 570 for an NDA from ——————————— The DMF was found to be inadequate. Two deficiencies were cited in a letter dated 2/22/02. The company responded to these deficiencies on 6/20/2002. The responses to these deficiencies were reviewed and found to be adequate by this reviewer.

Drug Product:

Advil® Allergy Sinus Caplet is an orange colored caplet, containing 200 mg of ibuprofen, 30 mg of pseudoephedrin hydrochloride and 2 mg of chlorpheniramine maleate. The drug product will be marketed in a child reistance blister and a child resistance pouch.

The DP is made by —— One —— lot contains ibuprofen only. The other lot contains the other two ingredients pseudoephedrine hydrochloride and chlorpheniramine maleate. —— The caplets are coated with Opadry Orange II and printed "Advil A/S" (for Advil allergy/sinus) in black ink on one side of the caplet.

The manufacture of these caplets is a fairly standard manufacturing process. Therefore no critical manufacturing steps have been identified by the firm in the manufacture of the DP.

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

The DP is intended for oral administration. Ibuprofen is an analgesic, pseudoephedrine hydrochloride is a decongestant and chlorpheniramine maleate is an antihistamine.

The firm is requesting a 24 month expiration dating for the drug product stored at room temperature (25° C/60% RH) in both container/closure configurations. With the submission of satisfactory —— room temperature stability data on three batches packaged in each container closure system —— expiration date can be granted.

C. Basis for Approvability or Not-Approval Recommendation

The three drug substances are USP articles and have been in use for a long time.

The manufacture of the dosage form does not involve any unusual measures to be taken. The stability of the dosage form over 12 months does not show any instability trends that would be cause for alarm. The applicant was asked by the pharmacokineticist to tighten the dissolution specifications, and by this reviewer to tighten the specifications for total amides. The company has complied with both these requests.

The company had reservations about meeting the acceptance criterion for ——as an unspecified impurity, and a number of discussions were held with the company over this issue in the last week of the review cycle.

This matter was resolved on the last day of the review as a result of negotiations between the company and Dr. Smith and this reviewer. At the suggestion of Dr. Smith, the company agreed to re-classify this degradation product as a specified impurity and an acceptance criterion was agreed upon.

During these last-minute negotiations the company also indicated that it wished to include the—— of ibuprofen-pseudoephedrine as a specified impurity and proposed limits for this degradant. Even though this proposal was made in the last minutes of the negotiations, it was considered and accepted by the Agency.

There are three drug-substance manufacturing facilities and two facilities related to the manufacture, release testing, packaging and stability testing of the drug product. All of these facilities were found to be acceptable. An overall "Acceptable" recommendation was issued by Compliance on 7/16/02.

The company has asked for a categorical exclusion under the provisions of 21 CFR 25.3(a), which is acceptable.

III. Administrative

A. Reviewer's Signature: N/A

B. Endosement Block: N/A

C. CC Block: N/A

WITHHOLD 48 PAGE (S)

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

/s/

Vispi Bhavnagri
12/12/02 01:19:07 PM
CHEMIST

John Smith
12/12/02 01:25:15 PM
CHEMIST