CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-374

CHEMISTRY REVIEW(S)

NDA 21-374

Advil Cold & Sinus (Ibuprofen/Pseudoephedrine) Liquigels

Whitehall-Robins Healthcare

Rao Puttagunta, Ph.D.
Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs

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Chemistry Review Data Sheet

1. NDA #: 21-374

2. REVIEW #: 1

3. REVIEW DATE: 18-APR-2002

4. REVIEWER: **Rao Puttagunta**

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	24-JUL-2001
Amendment 1	24-AUG-2001
Amendment 2	24-JAN-2002
Amendment 3	15-APR-2002
Amendment 4	25-APR-2002
Amendment 5	29-APR-2002
Amendment 6	02-MAY-2002
Amendment 7	17-MAY-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Wyeth Consumer Healthcare
Address:	5 Giralda Farms, Madison, NJ 07940
Representative:	David S. Smith, Ph.D., Director, Regulatory Affairs
Telephone:	973-660-6806

8. DRUG PRODUCT NAME/CODE/TYPE:

a) **Proprietary Name:** Advil Cold & Sinus Liquigels
b) **Non-Proprietary Name (USAN):** Ibuprofen/Pseudoephedrine HCA
c) **Code Name/#:** N/A
d) **Chem. Type/Submission Priority:**

- **Chem. Type:** 3
- **Submission Priority:** S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Pain Reliever/Fever Reducer/Nasal decongestant

11. DOSAGE FORM: Capsule, Liquid Filled

12. STRENGTH/POTENCY: Ibuprofen 200 mg/Pseudoephedrine HCl 30 mg per capsule

13. ROUTE OF ADMINISTRATION: Oral

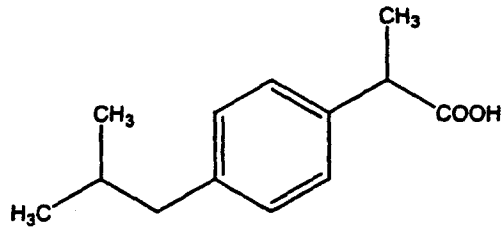
14. Rx/OTC DISPENSED: ___Rx _X_OTC

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

_____SPOTS product – Form Completed

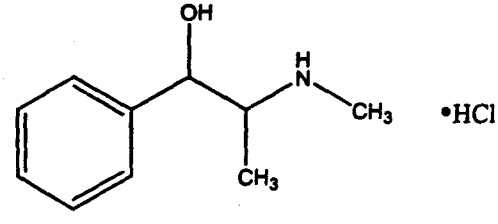
__X___Not a SPOTS product

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



Ibuprofen

(±)-2-(p-Isobutylphenyl)propionic acid, $C_{13}H_{18}O_2$, Mol. Wt. 206.28



Pseudoephedrine hydrochloride

(+)-α-[1-(methylamino)ethyl] benzenemethanol hydrochloride, $C_{10}H_{15}NO{\cdot}HCl$, Mol. Wt. 201.69

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	9/07/01	
	II			3	Adequate	11/08/01	
	III			7	N/A		Complies with 21 CFR § 177.1380, 175.105, and 175.300 (See page 31)
	III			3	Adequate	6/14/00	
	III			3	Adequate	9/21/00	
	II	R.P. Scherer	Drug Product	7	N/A		See page 12

[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		Advil Cold & Sinus Liquigels

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	06-MAY-2002	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Pending	Initiated on 20-MAY-2002	
OPDRA	N/A		
EA	Categorical Exclusion		
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-374

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry standpoint this NDA is recommended for approval.

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:

———

Pseudoephedrine HCl:

———

2) Drug Product:

The Advil Cold & Sinus Liquigels (liquid filled soft gelatin capsules) contain ibuprofen 200 mg and pseudoephedrine HCl 30 mg per capsule.

A description of the drug product manufacturing process is included. In-process acceptance criteria such as moisture content, fill-weight, ribbon thickness, and seal thickness are established to insure consistency in product quality.

The drug product is packaged in child-resistant blisters. The submitted drug product stability data include long-term stability data for ——— and accelerated stability data for ——— The applicant proposed a 24-month expiration period.

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

The Advil Cold & Sinus Liquigels (liquid filled soft gelatin capsules) are orally administered for temporary relief of the symptoms associated with common cold, sinusitis or flu. The Advil Cold & Sinus Liquigels are supplied in cartons of 16 and 32 unit doses. Each capsule contains ibuprofen 200 mg and pseudoephedrine HCl 30 mg. Dosing schedule is 1 capsule every 4 to 6 hours and the maximum daily dose is 6 capsules.

Recommended storage conditions: 20-25°C (68-77°F).

C. Basis for Approvability or Not-Approval Recommendation

The CMC information of the drug substances ibuprofen and pseudoephedrine HCl was referenced to the DMFs ——— respectively. These DMFs have been recently reviewed and found adequate. Since both the drug substances are compendial items they are tested according to the USP specifications.

Appropriate in-process, release and stability acceptance criteria have been established for the drug product to insure consistency in quality. The packaging materials were found adequate. The drug product specification was considered adequate after the applicant submitted a justification for the proposed acceptance criteria and the reviewer's discussion with the PharmTox reviewer.

The submitted drug product stability data for ——— conform to the established acceptance criteria. The submitted stability data and statistical analysis were considered adequate to support proposed expiration dating period of 24 months.

The proposed dissolution acceptance criterion of ———) in 30 minutes is acceptable to the biopharm reviewer.

It is stated that the gelatin used for the manufacture of Advil Cold and Sinus soft gelatin capsules is prepared from ——— (amendment dated 4/25/02).

The NDA 21-374 is recommended for approval based on the submitted CMC information.

III. Administrative

A. Reviewer's Signature N/A

B. Endorsement Block N/A

C. CC Block N/A

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

28 pages