CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-441

ADMINISTRATIVE DOCUMENTS

ITEM 14: PATENT CERTIFICATION

The undersigned declares that U.S. Patent Nos. 4,619,934 and 5,025,019 cover the formulation, composition and/or method of use of Advil® Allergy Sinus caplets. This product is the subject of this application for which approval is being sought.

WHITEHALL-ROBINS HEALTHCARE

Steven H. Flynn
Patent Counsel

ITEM 13: PATENT INFORMATION

Pursuant to 21 CFR 314.53, Whitehall-Robins Healthcare herewith submits patent and exclusivity information for Advil® Allergy Sinus (ibuprofen 200 mg, pseudoephedrine HCl 30 mg, chlorpheniramine maleate 2 mg) caplets. The purpose of this submission is to obtain approval of this combination pain reliever, nasal decongestant, and antihistamine drug product. The proposed indication for this product is "temporary relief of the following symptoms associated with hay fever or other respiratory allergies, and sinusitis: minor aches and pains, headaches, runny nose, sneezing, itchy, watery eyes, itching of the nose or throat, nasal congestion, and sinus pain and pressure". Please note that the product is also referred to as Advil® Multi-Symptom Allergy Sinus in various documents.

The undersigned declares that U.S. Patent Nos. 4,619,934 and 5,025,019 cover this combination of ibuprofen, pseudoephedrine and chlorpheniramine. Whitehall-Robins Healthcare has license rights to the patents.

Whitehall-Robins Healthcare is hereby including the patent and exclusivity information (Exhibit A) for this NDA.

WHITEHALL-ROBINS HEALTHCARE

Steven H. Flynn
Patent Counsel

APPEARS THIS WAY
ON ORIGINAL

Exhibit A: Patent/Exclusivity Information

1) Active Ingredient	Ibuprofen / pseudoephedrine HCl / chlorpheniramine maleate
2) Strength	200 mg / 30 mg / 2 mg
3) Trade Name	Advil® Allergy Sinus
4) Dosage Form, Route of Administration	Caplets, Oral
5) Applicant Firm Name	Whitehall-Robins Healthcare, Division of American Home Products Corporation
6) NDA Number	21-441
7) Approval Date	Pending
8) Exclusivity – Date first ANDA could be approved and length of exclusivity period	Pursuant to clause (iii) of Section 505 (j)(4)(D) and clause (iii) of Section 505 (c)(3)(D) of the Federal Food, Drug and Cosmetic Act, as amended, no ANDA may be approved and made effective prior to three (3) years after the date of approval of this NDA. This NDA contains "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application" included in the data submitted to support the following indication:
9) Applicable Patent Information	U.S. Patent No. 4,619,934 Expires: April 9, 2004 Type: Drug Product, Method of Use Owner: The Proctor & Gamble Company U.S. Patent No. 5,025,019 Expires: June 18, 2008 Type: Drug Product, Method of Use Owner: The Proctor & Gamble Company

EXCLUSIVITY SUMMARY for NDA #: 21-441 SUPPL # _____

Trade Name: Advil Allergy Sinus Caplet

Generic Name: ibuprofen 200 mg, pseudoephedrine 30 mg, chlorpheniramine, 2 mg

Applicant Name: Wyeth Consumer Healthcare HFD-550

Approval Date: December 17, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/_X_/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /_X_/

If yes, what type(SE1, SE2, etc.)? _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # AD-99-01

Investigation #2, Study # AD-99-02

Investigation #3, Study # AD-99-03

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # **AD-99-01**

Investigation #__, Study # **AD-99-02**

Investigation #__, Study # **AD-99-03**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # **61,725** YES /**X**/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

/S/ RN, 175pl 12/18/02

Signature of Preparer Date

Title: **Regulatory Health Project Mananger**

/S/ 12/19/02

Signature of Division Director Date

/S/ 12/19/2

Signature of Division Director Date

cc:
Archival NDA 21-441
HFD-550/Division File
HFD-560/Division File
HFD-550/RPM
HFD-560/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

APPEARS THIS WAY
ON ORIGINAL

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-441 Supplement Type (e.g. SE5): x Supplement Number: x

Stamp Date: 2/28/02 Action Date: 12/31/02

HFD 550 Trade and generic names/dosage form: ibuprofen 200mg/pseudoephedrine 30 mg/chlorpheniramine 2 mg caplet

Applicant: Wyeth Consumer Healthcare Therapeutic Class: 4S

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold

Is there a full waiver for this indication (check one)?

☐ YES: Please proceed to Section A.

X No: Please check all that apply: ___Partial Waiver _X_Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns

- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- _X_ Adult studies ready for approval
- ☐ Formulation needed

Other: Pediatric studies being done under IND 63,999
Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

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

/s/

Jane Dean
12/19/02 10:13:34 AM

IV. ENVIRONMENTAL ASSESSMENT

Enclosed is a Statement of Compliance to support categorical exclusion from an environmental assessment.

January 4, 2001

Environmental Assessment

Statement of Compliance

Whitehall-Robins Healthcare states that an Environmental Assessment (EA) for the proposed action on the NDA for Advil® Allergy Sinus Tablets (ibuprofen 200 mg / pseudoephedrine HCl 30 mg / chlorpheniramine maleate 2 mg), is categorically excluded according to 21 CFR 25.31(a).

The aforementioned regulation states that a categorical exclusion is permitted for "Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety." The proposed action does not increase the use of the active moiety. Advil® Allergy Sinus Tablets is a combination drug which contains active ingredients (ibuprofen 200 mg / pseudoephedrine HCl 30 mg / chlorpheniramine maleate 2 mg) that are currently used in other marketed products. For example, ibuprofen 200 mg is currently used in Advil® Liquigels. Pseudoephedrine HCl and chlorpheniramine maleate are used in numerous combination products under the applicable OTC monograph 21 CFR 338 (e.g. Allerest®).

To the best knowledge of Whitehall-Robins Healthcare, no extraordinary circumstances exist associated with the proposed action.

Richard A. Constable
Director, Global EH&S Compliance
Wyeth-Ayerst Pharmaceuticals

Ken Warner
Director, Regulatory Affairs CMC
Whitehall-Robins Healthcare

ITEM 16: DEBARMENT STATEMENT

Whitehall-Robins Healthcare hereby certifies that it did not and will not use in any capacity the services of any person debarred under Sections 306 of the Act in connection with such application.

WHITEHALL-ROBINS HEALTHCARE

Sharon Heddish

Sharon C. Heddish
Vice President
Regulatory Affairs, Worldwide

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list.	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mary Davis	Director, Regulatory Affairs
FIRM/ORGANIZATION	
Whitehall-Robins Healthcare	
SIGNATURE	**DATE**
Mary H Davis	2/28/2002

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

WITHHOLD 4 PAGE (S)

APPENDIX 2-N

NDA ROUTING LOG

SPONSOR: Whitehall-Robins Healthcare

DRUG: Advil (Ibuprofen/Pseudoephedrine/Chlorpheniramine Maleate) Allergy Sinus Caplet

INDICATION: Allergic Rhinitis

NDA NUMBER: 21-441 DIVISION: 550 FORM 5:
DATE REC: 01 MAY 02 DATE SENT: 04 MAY 02 NEW REG. NDA:
PRE- ASSIGNED: ✓ PRE-SUB: FOLLOW-UP SHIPMENT:

COPIES RECEIVED, STORED AND SENT

BLUE ACHIVAL-2626 (ALL COPIES SENT TO DIVISION)	RECV: 1·1 ✓ SENT: 1·1 STOR:
ORANGE PHARMACOKINETICS REVIEW-2626C (FORM 2817)	RECV: 1·8 - 1·17 ✓ SENT: 1·8 - 1·17 STOR:
GREEN STATISTICAL REVIEW-2626F (FORM 2817)	RECV: SENT: STOR:
TAN CLINICAL REVIEW-2626E (FORM 2817)	RECV: 1·18 - 1·34 ✓ SENT: 1·18 - 1·34 STOR:
RED CHEMISTS REVIEW-HFD-095 (ALL COPIES SENT TO DIVISON) (FORM 1706)	RECV: 1·2 - 1·6 ?? SENT: 1·2 - 1·6 STOR:
YELLOW PHARMACOLOGY REVIEW (2626B ALL COPIES SENT TO DIVISION)	RECV: 1·7 SENT: 1·7 STOR:
WHITE MICROBIOLOGY REVIEW-2626D (ALL COPIES SENT TO DIVISION)	RECV: SENT: STOR:

COMMENTS: X 1·1, X1·1A Sent to EDR

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA **21-441**	Efficacy Supplement Type SE-	Supplement Number
Drug: **Advil Allergy Sinus Caplet (ibuprofen 200 mg, pseudoephedrine 30 mg, chlorpheniramine 2 mg)**	Applicant: **Wyeth Consumer Healthcare (fdba Whitehall-Robins Healthcare)**	
RPM: **Jane A. Dean, RN, MSN**	HFD-**550**	Phone # **301-827-2536**
Application Type: **(X)** 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): **NA**	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	4
• Other (e.g., orphan, OTC)	OTC
❖ User Fee Goal Dates	January 1, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	NA
• OC clearance for approval	NA
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	X

Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	NA
General Information	
❖ Actions	
• Proposed action	(X)AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS: November 11, 2002 OTC: September 30, 2002 November 5, 2002 November 25, 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X
• Pre-NDA meeting (indicate date)	November 29, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA
❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**December 23, 2002**
❖ Clinical review(s) *(indicate date for each review)*	**December 23, 2002**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**NA**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**December 23, 2002 Clinical Review**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**X**
❖ Statistical review(s) *(indicate date for each review)*	**December 16, 2002**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**August 9, 2002** **October 7, 2002** **October 7, 2002**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**NA**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**November 8, 2002** **December 10, 2002**
• Bioequivalence studies	**November 22, 2002**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**December 12, 2002**
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**December 12, 2002**
• Review & FONSI *(indicate date of review)*	**NA**
• Review & Environmental Impact Statement *(indicate date of each review)*	**NA**
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**NA**
❖ Facilities inspection (provide EER report)	Date completed: **July 16, 2002** **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**(X)** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**NDA 19-771: November 22, 1988** **IND 61,725: January 6, 2001** **NDA 21-441: October 18, 2002**
❖ Nonclinical inspection review summary	**NA**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**NA**
❖ CAC/ECAC report	**NA**

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/s/

Jane Dean
1/2/03 05:38:25 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No 0910-0297
Expiration Date. February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Whitehall Robins Healthcare
5 Giralda Farms
Madison, New Jersey 07940

RECEIVED
MAR 0 4 2002
MEGA/CDER

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 660-5753

3. PRODUCT NAME

Advil® Allergy Sinus

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-441

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW.

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4214

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Sharon Heddish Sharon Heddish	Vice President	1/2/02

FORM FDA 3397 (4/01)

WITHHOLD 1 PAGE (S)

Team Leader's Memorandum: NDA 21-441
Advil Allergy Sinus Tablets (Wyeth Consumer Healthcare)
(ibuprofen 200 mg/pseudoephedrine HCL 30 mg/chlorpheniramine 2 mg)
12/20/2002

Submitted:
This NDA represents the first triple combination product for OTC use that contains the ingredients noted above. Issues discussed at pre-NDA meetings included design issues to substantiate the analgesic contribution of ibuprofen in this particular setting i.e. in subjects suffering from seasonal allergic rhinitis. A single study (AD-99-02) was submitted to demonstrate efficacy that involved a total of 1070 subjects. This placebo-controlled, one-week trial had two dosing arms of the triple combination (i.e. one or two tabs q 4-6 hours, not to exceed 6 tablets in 24 hours, to evaluate the lowest effective dose) and had an arm that did not contain ibuprofen (to evaluate the contribution of the other two ingredients); a full factorial study was not conducted in that the other two ingredients are monographed. Two other studies in the NDA were PK studies. Safety consisted of all the studies noted above plus a review of FDA and Sponsor adverse events reported on the triple combination and any literature available on the combination of these products. Since the dose of chlorpheniramine was utilized that was below the monographed dose, a consult to the HFD-570 (pulmonary) was requested for this NDA.

Review of the efficacy and safety was conducted by Dr.Christina Fang (HFD-550). In her opinion, the data in this NDA demonstrated sufficient efficacy and adequate safety to allow for the availability of this product for OTC use.

Discussion/Recommendations:
Without a full factorial design in the submitted study (AD-99-02), it difficult to arrive at robust conclusions regarding efficacy. This problem is confounded by the absence of a "usage" study which are often part of OTC applications. The conclusion that there is no statistically significant difference in the efficacy of one vs. two tabs of this triple formulation lessens the clinical concerns for the safety of this combination for OTC usage.

Ingestion of triple combinations, designed to treat an array of symptoms, do not allow titration of any single ingredient to treat any individual symptom. Therefore, patients/consumers who take these combinations will already have three separate drugs on board which then will be increased should they decide to exceed the labeled doses to treat a symptom (s). There is evidence in this NDA to suggest that adverse events with two vs. one tab increase although it is not possible to delineate which of the three ingredients is responsible for any particular adverse event due to the lack of a full factorial design. These combinations have the potential to interact not only with the other ingredients in the combination but also with the potential myriad of other OTC and prescription drugs which may contain the same or similar drugs to those in the combination adding to their safety risk as well as other risks from other combinations. To confound matters, these mixtures can then be added to by consumers utilizing non-FDA approved alternatives.

It is probably the case that adverse events associated with any of the "monographed" ingredients in this triple combination are often times not reported to health care authorities, such as FDA, or will be attributed to other medications that patients/consumers take for other reasons. Therefore, an absence of evidence to suggest an significant adverse events in this very limited safety evaluation of this NDA for this triple combination product, is not evidence of absence of an important safety signal. In fact, there are worrisome suggestions in this NDA (i.e. literature reports of aplastic anemia associated with chlorpheniramine) that there may well be important safety concerns associated with one or more components of this triple combination alone. There is, at present, no robust safety information (in particular, in this NDA) on all three ingredients and none addressing the use of this product in a real setting with patients/consumers taking their other medications.

There is no clear evidence to suggest that the efficacy and safety of this triple combination results in an unfavorable risk-benefit for the proposed OTC use and so it will be approved. However, the trend toward increasingly complex mixtures (triple combinations) of products allowed for OTC use appears to be a worrisome combination of confusing efficacy endpoints and blurring of safety reporting. This trend needs to be seriously considered in the future.

James Witter MD, PhD
Clinical Team Leader
Division of Anti-inflammatory, analgesic and ophthalmic drug products (HFD-550)

APPEARS THIS WAY

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/s/

James Witter
12/23/02 11:20:14 AM
MEDICAL OFFICER
TL memorandum

Lee Simon
1/2/03 04:56:08 PM
MEDICAL OFFICER

OTC Drug Labeling Review
for Advil Allergy Sinus

Division of Over-The-Counter Drug Products • HFD-560
Center for Drug Evaluation and Research • Food and Drug Administration
Rockville • MD 20857

NDA:	21-441
Sponsor:	Wyeth Consumer Healthcare
Drug Product:	Advil Allergy Sinus Tablets
Active Ingredient(s):	200 mg ibuprofen, 30 mg pseudoephedrine HCl, 2 mg Chlorpheniramine maleate
Indication(s):	relieves runny nose; nasal congestion; sneezing; itchy, watery eyes; headache; and sinus pressure
Pharmacological Class:	internal analgesic/antipyretic, nasal decongestant, antihistamine
Stock Keeping Units:	10-, 20-, 40-count carton and 1-count pouch
Submission Date:	December 18, 2002
Review Date:	December 19, 2002
Project Manager:	Elaine Abraham, R. Ph.
Reviewer:	Matthew R. Holman, Ph.D.

BACKGROUND

The sponsor submitted 40-count color mock-up label in response to the Agency's comments provided via telephone conversations of 12/17 and 12/18 with OTC staff. The sponsor further committed that the same revisions will be made to all package sizes (10's, 20's, 40's, pouch and dispenser).

WITHHOLD 1 PAGE (S)

REVIEWER'S COMMENTS

The sponsor has revised the 40-count carton label to incorporate all of the recommendations by the Agency and also committed that the same revisions will be made to all package sizes (10's, 20's, 40's, pouch an dispenser). These revised labels will be implemented once inventories of launch labeling have been exhausted. This is acceptable.

RECOMMENDATION

An approval action can be issued to the sponsor based on the submitted 40-count label and the sponsor's commitment that the same revisions will be made to all package sizes (10's. 20's, 40's, pouch and dispenser). The sponsor also commits to implement these revised labels once inventories of launch labeling have been exhausted.

/S/

Matthew R. Holman, Ph.D.
Interdisciplinary Scientist, HFD-560

/S/

Marina Chang, R.Ph.
IDS Team Leader, HFD-560

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/s/

Matthew Holman
12/19/02 03:22:10 PM
INTERDISCIPLINARY

Marina Chang
12/19/02 03:25:14 PM
INTERDISCIPLINARY

From: Filomena Gesek [GesekF@wyeth.com]
Sent: Tuesday, November 26, 2002 1:46 PM
To: deanj@cder.fda.gov
Cc: fangc@cder.fda.gov
Subject: NDA 21-441
Ms. Dean:

In your absence, I placed a call to Dr. Fang to assure she had received the fax which included the information requested in your 25 November fax. The following summary is provided in response to Dr. Fang's request, for your reference.

Filomena Gesek
Associate Dir. Regulatory Affairs
Wyeth Consumer Healthcare

SUBJECT NDA 21-441: Medical Officer Question

A phone call was placed to Dr. C. Fang to assure that she received a fax in response to Ms. J. Dean's fax of 25 November 2002. Our fax responded to Dr. Fang's request .

Dr. Fang acknowledged that she had received the MedWatch forms for each case.

I asked her of the significance for the request and whether there was something in particular she was concerned about. D. Smith mentioned that

She noted that she would like to get safety information on products She suggested obtaining worldwide safety surveillance data and literature search information.

D. Smith explained that we've accumulated safety data for multiple combinations in the past and that our plan is to update and build upon this information for He noted that we have not done this for We are adding ibuprofen to an existing combination product. Therefore, our safety update will be specific to the ibuprofen combination.

Dr. Fang said she was looking for information on patterns of use, abuse potential and other risks associated with products that have multiple active ingredients including D. Smith responded that we've detected no patterns and most safety problems stem from inappropriate product use. Dr. Fang noted that she understood our position.

Dr. Fang asked that in the absence of the CSO, we send the Agency a brief summary of the conversation. We agreed, thanked her for her time and ended the call.

"MMS <wyeth.com>" made the following
annotations on 11/26/02 13:47:00

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/s/

Jane Dean
12/6/02 05:41:35 PM
CSO

Division of OTC Drug Products Labeling Review
Addendum Review

NDA #: 21-441

Submission Date: 10/24/02
Review Date: 11/05/02

APPLICANT'S: Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

APPLICANT'S REPRESENTATIVE: Filomena Gesek
Assoc. Dir., Regulatory Affairs
Wyeth Consumer Healthcare

DRUG: Advil Allergy Sinus Caplet
(ibuprofen 200mg, pseudoephedrine hydrochloride 30mg and chloropheniramine maleate 2 mg coated tablet)

PHARMACOLOGIC CATEGORY: Pain reliever/fever reducer/nasal decongestant/ antihistamine

SUBMITTED: 10-counts carton label

BACKGROUND:

The sponsor submitted, via e-mail, revised 10-counts carton label for an expedited review. This revised carton label has been revised to address all of the comments in the Agency's 10/07/02 fax that pertains to the proposed carton and blister pack labels. It will consider the feedback provided by the Agency when revising the other package sizes. In this submission, the sponsor has proactively included the warnings in the proposed rule to amend the TFM to include ibuprofen in the OTC internal analgesics monograph (published 8/21/02). It also added a stomach bleeding based on recommendations made at the recent (09/20/02) NDAC meeting.

REVIEWER'S COMMENT:

1. Principle Display Label (PDP)

   The sponsor has revised the PDP as requested by the Agency. However, it added "headache" to the promotional claim. This is acceptable. It also included an arrow pointing to the caplet, with the statement ' This statement is unacceptable. It is inconsistent with the "Directions" which states " One caplet every 4-6 hours, while symptoms persist".

The sponsor added the established name to proceed the pharmacological category for each respected ingredient. However, the yellow lettering on a green background makes the information difficult to read. The sponsor should change the color scheme of these statements to a more readable presentation (e.g., white lettering on a green background).

2. The side panels - acceptable.

3. "Drug Facts" Panel

   a. Under "Warnings" - the sponsor included the warnings, with modifications, proposed in the rule to amend the TFM to include ibuprofen in the OTC internal analgesics monograph (published 8/21/02). The deviations from the proposed rule were to minimize redundancy. It also added a stomach bleeding based on recommendations made at the recent (09/20/02) NDAC meeting. These changes are acceptable.

   b. Under "Warnings, Do not use" - debold the phrase "if you". Only the subheading "Do not use" needs to be bolded.

   c. Under "Directions, [redacted]. For consistency with currently marketed products, in the fax dated 10/7/02, the Agency requested the sponsor to include this statement to the label. After re-consideration of the submitted data which shows no significant efficacy difference between the one-caplet and two-caplet dose, but an increase of adverse events, the Agency is now requesting this statement (i.e., [redacted] to be deleted.

   d. The sponsor did not vertically align the bulleted statements in numerous sections of the "Drug Facts" (e.g., "Uses", "Warnings - Do not use, Ask a doctor before use and Ask a doctor or pharmacist before use"). This is unacceptable. "...Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line." [21 CFR 201.66 (d)(4)

RECOMMENDATIONS:

1. Request the sponsor to further revise the carton label as follows:

   a. Principal Display Panel: The arrow pointing to the caplet, with the statement [redacted] is unacceptable. It is inconsistent with the "Directions" which states " One caplet every 4-6 hours, while symptoms persist". Please delete this arrow or revise to be the same as stated in the "Directions".

   b. "Drug Facts" Panel:

(i) Under "Warnings, Do not use" - the phrase "if you" in the subheading should not be bolded.

(ii) Under "Directions" - delete the second sentence (i.e., [redacted] This deletion is required because there is an increase in adverse events with the two-caplet dose and no significant efficacy difference between the one-caplet dose.

(iii) The bulleted statements in numerous sections of the "Drug Facts" (e.g., "Uses", "Warnings - Do not use, Ask a doctor before use and Ask a doctor or pharmacist before use") are not vertically aligned. 21 CFR 201.66 (d)(4) states that "...Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line."

2. Inform the sponsor that the Agency currently is accepting the sponsor's proposed warnings, with modifications, to the proposed rule to amend the TFM to include ibuprofen in the OTC internal analgesics monograph (published 8/21/02). The sponsor stated that the deviations from the proposed rule were to minimize redundancy. The Agency will accept the proposed stomach bleeding warning based on recommendations made at the recent (09/20/02) NDAC meeting. However, the Advisory Committee's recommendations have not been fully evaluated by the Agency. It is understood that the use of this stomach warning and the proposed ibuprofen warnings is at the sponsor's risk, the risk being that the sponsor must revise these statements and to be in compliance with any final regulations issued.

3. The Agency recommends the sponsor to change the color scheme in the presentation of the established name and the pharmacological category statements to a more readable color scheme (e.g., white lettering on green background).

4. Request the sponsor to submit all SKU labels for our review and comment prior to the action letter.

/S/

Marina Y. Chang, R. Ph.

/S/

concur, Debbie Lumpkins

APPEARS THIS WAY

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/s/

Marina Chang
11/7/02 02:01:23 PM
INTERDISCIPLINARY

Debbie Lumpkins
11/7/02 03:01:17 PM
INTERDISCIPLINARY

Division of OTC Drug Products Labeling Review
2nd- Addendum Review

NDA #: 21-441

Submission Date: 11/25/02
Review Date: 11/25/02

APPLICANT	Wyeth Consumer Healthcare Five Giralda Farms Madison, NJ 07940
APPLICANT'S REPRESENTATIVE:	Filomena Gesek Assoc. Dir., Regulatory Affairs Wyeth Consumer Healthcare
DRUG:	Advil Allergy Sinus Caplet (ibuprofen 200mg, pseudoephedrine hydrochloride 30mg and chloropheniramine maleate 2 mg coated tablet)
PHARMACOLOGIC CATEGORY:	Pain reliever/fever reducer/nasal decongestant/ antihistamine
SUBMITTED:	10s, 20s and 40s count carton labels Blister pack of 10s Pouch of 2s Pouch dispenser

BACKGROUND:

The sponsor submitted color mock-up labels in response to the Agency's comments outlined in 10/7 and 11/8 facsimiles and to telephone conversations of 11/4 and 11/12 with OTC staff.

REVIEWER'S COMMENT:

The sponsor has made the changes as requested by the Agency and the color mock-up labels are acceptable. The "Drug Facts" specifications for format, font and type sizes are in compliance with 21 CFR 201.66.

The sponsor indicated that it will consider adding a ——— section to the "Drug Facts" at a future date. This is acceptable.

The Advil Allergy Sinus pouch, which contains one dose of the product (i.e., 1 caplet), is not presented in conformance with "Drug Facts" format requirement.

This is based on FDA's April 5, 2002, Federal Register publication granting a partial stay in compliance for "convenience size" OTC drug products until further notice. The sponsor indicated that once the Agency publishes rulemaking to modify the labeling requirements for "convenience size" OTC drug products, it will make the changes necessary to comply with the rule. This is acceptable.

RECOMMENDATION:

1. An **APPROVAL** letter can be issued to the sponsor for the 10s, 20s and 40s carton label and blister pack, sample pouch of 2s, and pouch dispenser.

2. Request the sponsor to submit final printed labels identical to the labels included with this submission, when available.

3. Inform the sponsor that the Agency currently is accepting the sponsor's proposed warnings, with modifications, to the proposed rule to amend the TFM to include ibuprofen in the OTC internal analgesic monograph (published 8/21/02). The Agency will also accept the proposed stomach bleeding warning based on recommendations made at the recent (09/20/02) NDAC meeting. It is understood that the use of the proposed ibuprofen and stomach warnings is at the sponsor's risk, subject to final regulations issued.

/S/

Marina Y. Chang, R. Ph.

/S/

concur. Debbie Lumpkins

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/s/

Marina Chang
12/3/02 07:36:15 AM
INTERDISCIPLINARY

Debbie Lumpkins
12/3/02 11:01:18 AM
INTERDISCIPLINARY

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Dr. Julia Kim	**From:** Ms. Jane A. Dean, RN, MSN
Fax: 973-660-8660	**Fax:** 301-827-2531
Phone: 973-660-5139	**Phone:** 301-827-2090
Pages: 1 (including cover page)	**Date:** 30 October 2002
Re: NDA 21-441 CMC Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Dr. Kim,

Dr. Bhavnagri has requested the following information please.

- Please tighten your acceptance criteria for MAPP and total amides in the tablets and provide a justification for the new limits.

Feel free to call me if you have any questions at 301-827-2536.

Sincerely,

Jane A. Dean
Project Manager

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ON ORIGINAL

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/s/

Jane Dean
10/31/02 03:46:51 PM
CSO

MEMORANDUM

Date: 23 October 2002

To: Christina Fang, M.D.
Medical Officer
Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, HFD-550

From: Charles E. Lee, M.D.
Medical Officer
Division of Pulmonary and Allergy Drug Products, HFD-570

Through: Mary E. Purucker, M.D., Ph.D.
Medical Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570

Badrul A. Chowdhury, M.D., Ph.D.
Acting Director
Division of Pulmonary and Allergy Drug Products, HFD-570

Subject: Medical Officer Consultation
NDA 21-441 for ibuprofen 200 mg/pseudoephedrine 30 mg/chlorpheniramine 2 mg, Advil® Allergy Sinus

Materials: NDA 21-441, N-000, 28 February 2002, electronic submission

Request for consultation to Division of Pulmonary and Allergy DrugProducts, HFD-570, 22 April 2002

1. EXECUTIVE SUMMARY

This study supports the efficacy and safety of ibuprofen 200 mg/pseudoephedrine 30 mg/chlorpheniramine 2 mg in subjects with seasonal allergic rhinitis, and supports the contribution of ibuprofen to the efficacy of ibuprofen /pseudoephedrine/chlorpheniramine (IB/PSE/CPM). This review is not able to assess the contribution of CPM or PSE/CPM to the combination product because the appropriate active controls needed to assess the contribution of PSE and CPM were not included in this study. The minimum effective dose of the product is IB 200 mg/30 mg PSE/2 mg CPM. This dose was statistically superior to placebo for relief of allergy symptoms and of allergy-associated headache, facial pain/pressure/discomfort. There is no added efficacy with IB 400 mg/ PSE 60 mg/CPM 4 mg and there is a dose-related increase in AEs with the higher dose. The study supports the sponsor's proposed dose of 1 tablet (IB 200 mg/PSE 30 mg/CPM 2 mg) every 4-6 hours.

2. BACKGROUND

The Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP) has requested a consultation regarding NDA 21-441 for a ibuprofen 200 mg/pseudoephedrine HCl 30 mg/chlorpheniramine maleate 2 mg over-the-counter (OTC) product. The proposed trade name is Advil® Allergy Sinus. The sponsor is Whitehall-Robins Healthcare. The proposed indication is for [redacted] The product is proposed for use in adults and children 12 years of age and older. The dosage form is a capsule-shaped tablet ("caplet"). The proposed dose is 1 tablet (ibuprofen 200 mg/pseudoephedrine HCl 30 mg/chlorpheniramine maleate 2 mg) every 4-6 hours while symptoms occur. The consumer is not to take more than 6 tablets in any 24-hour period unless directed by a doctor (maximum total daily dose = ibuprofen 1200 mg/pseudoephedrine HCl 180 mg/chlorpheniramine maleate 12 mg) [summary/summary.pdf, pages 3-11-3 to 3-11-6, 3-11-20].

The sponsor refers to the NDA for their Advil® Cold & Sinus OTC product (NDA 19-771) for safety information supporting the safe over-the-counter use of an ibuprofen (IB) 200 mg/pseudoephedrine (PSE) 30 mg combination product. The Advil Cold & Sinus product is approved for the temporary relief of various symptoms associated with the common cold, sinusitis or flu at the dose of 1 tablet (IB 200 mg/PSE 30 mg combination product) every 4 to 6 hours. The consumer may use 2 tablets if symptoms do not respond to 1 tablet. The consumer is not to use more than 6 tablets in any 24-hour period (maximum total daily dose = 1200 mg IB/180 mg PSE). The dose of ibuprofen and PSE for the proposed IB/PSE/CPM product is the same as the recommended starting dose of their approved IB/PSE combination product [summary/summary.pdf, page 3-11-20].

Pseudoephedrine hydrochloride is also Generally Recognized As Safe and Effective (GRASE) for over-the-counter use individually or as a combination oral nasal decongestant ingredient with dosing to 240 mg/day for adults and children over 12 years (21 CFR 341.80(d)(1)(ii)).

Chlorpheniramine maleate is Generally Recognized As Safe and Effective (GRASE) for over-the-counter use as an individual or combination antihistamine ingredient in doses between 16 mg/day and 24 mg/day for adults and children over 12 years (21 CFR 341.72(d)(3)).

Reviewer comment:
The monograph dosing for CPM for adults and children ages 12 years and older is 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours. The proposed dose of CPM in the sponsor's product is ½ of that specified in the monograph. The sponsor's clinical program must support the efficacy of this dose of CPM.

Acceptable (Category I) combinations of Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic ingredients include simultaneous use of Category I single ingredient: oral nasal decongestants including pseudoephedrine; internal analgesic/antipyretics including aspirin and acetaminophen; and oral antihistamines including chlorpheniramine [summary/summary.pdf, page 3-11-20].

The sponsor's development plan was designed to demonstrate the following [summary/summary.pdf, page 3-11-24]:

- The safety and efficacy of the analgesic/decongestant/antihistaminic combination ibuprofen/pseudoephedrine hydrochloride/chlorpheniramine maleate in subjects with seasonal allergic rhinitis
- The contribution of ibuprofen to the analgesic and overall effectiveness of an ibuprofen/pseudoephedrine/chlorpheniramine combination in relieving the symptoms of seasonal allergic rhinitis
- The minimum effective dose of the combination
- The minimum effective dose of the antihistamine component.

Reviewer comment:
The consult has asked DPADP to consult on the contributing effect of PSE and CPM on allergy symptoms with emphasis on the contributing effect of CPM 2 mg. It should be noted that the sponsor's study was designed to assess the contribution of IB to the IB/PSE/CPM combination product, and so has included PSE/CPM as an active control. This study design is not able to assess the contribution of CPM, PSE, or PSE/CPM to the efficacy of the IB/SPE/CPM combination. If the desired objective was to assess the contribution of CPM to the efficacy of the IB/PSE/CPM combination, the appropriate active control should have been IB/PSE. If the desired objective was to assess the contribution of PSE/CPM to the efficacy of the IB/PSE/CPM combination, the appropriate active control should have been IB. If the desired objective was to assess the contribution of PSE to the efficacy of the IB/PSE/CPM combination, the appropriate active control should have been IB/CPM.

The appropriate active controls needed to assess the contribution of PSE and CPM were not included in this study. Accordingly, this review is not able to assess the contribution of CPM, PSE, or PSE/CPM to the combination product. This review will address the apparent contribution of IB to the IB/PSE/CPM product, as well as the overall efficacy of

the IB/PSE/CPM high dose and low dose regimens compared each other and with placebo.

The sponsor conducted a single efficacy and safety study AD-99-02 to achieve these objectives. DAOODP asks DPADP to review the efficacy and safety study AD-99-02 with respect to the effect of pseudoephedrine (PSE) and chlorpheniramine (CPM) on allergy symptoms with emphasis on the contributing effect of CPM 2 mg.

A review of clinical study AD-99-02 follows below.

3. CLINICAL STUDIES

The sponsor conducted one pivotal efficacy and safety study in support of this application.

3.1. AD-99-02: Advil multi-symptom allergy sinus efficacy and safety study

Conducted under: IND 61,725
Study dates: 2/13/01-7/11/01
Date of report: 1/29/02
[clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-2]

3.1.1. Summary and reviewer's conclusion of study results

This was a one-week, multi-center, multiple dose, double-blind, double-dummy, placebo-controlled, randomized, parallel-group, Phase 3 study performed in 49 centers. The objective of this study was to demonstrate the contribution of ibuprofen to the overall and analgesic effectiveness of IB/PSE/CPM in relieving the symptoms of SAR. The study was also to determine the minimum effective dose of the combination and the minimum effective dose of the antihistamine component of the combination. Treatment groups were 2 tablets of IB 200 mg/PSE 30 mg/CPM 2 mg (IB/PSE/CPM high dose), 1 tablet of IB 200 mg/PSE 30 mg/CPM 2 mg (IB/PSE/CPM low dose)
1 tablet of PSE 30 mg/CPM 2 mg (PSE/CPM active control), and placebo. Medication was dosed three times daily.

This study supports the efficacy of both IB/PSE/CPM high dose and IB/PSE/CPM low dose regimens tested. The primary efficacy variable was the change from baseline in the overall average total reflective symptom score (OATSS). Both IB/PSE/CPM high dose and IB/PSE/CPM low dose were statistically significantly superior to placebo and to PSE/CPM for the primary efficacy endpoint. Effect sizes expressed as difference from placebo were 9.9%, 9.1%, and 4.3% for IB/PSE/CPM high dose, IB/PSE/CPM low dose, and PSE/CPM, respectively. Primary efficacy endpoint results provide evidence of added efficacy from the IB component of the IB/PSE/CPM product for the OATSS endpoint. A key secondary efficacy variable was the time-weighted sum of the instantaneous pain intensity difference scores at 2 and 3 hours after the first dose of study medication (SPID3). Both IB/PSE/CPM high dose and IB/PSE/CPM low dose were statistically significantly superior to placebo and to PSE/CPM for SPID3. Effect sizes expressed as difference from placebo for the SPID3 were 26.3%, 26.7%, and 3.0% for IB/PSE/CPM

high dose, IB/PSE/CPM low dose, and PSE/CPM active control, respectively. Primary efficacy endpoint results provide evidence of added efficacy from the IB component of the IB/PSE/CPM product for the SPID3 endpoint. Neither OATSS nor SPID3 provided evidence of additional efficacy of IB/PSE/CPM high dose compared with IB/PSE/CPM low dose. Other secondary efficacy variables provide support for the efficacy of IB/PSE/CPM high dose and IB/PSE/CPM low dose. Other secondary efficacy variables also suggest that efficacy is added by IB in the IB/PSE/CPM combination, although it should be noted that there was no CMC information provided on the active control PSE/CPM product. Other secondary efficacy variables suggest that that IB/PSE/CPM high dose and IB/PSE/CPM low dose are equally efficacious.

This study supports the safety of IB/PSE/CPM high dose and IB/PSE/CPM low dose in the treatment of allergic rhinitis symptoms. There was adequate exposure to active drug to assess safety. AEs were fairly common. AEs were mild to moderate in intensity. AEs occurred more frequently in patients treated with IB/PSE/CPM high dose (68.0%), than in IB/PSE/CPM low dose (34.6%), PSE/CPM (36.2%), than in placebo (30.1%). The most common AEs noted in the IB/PSE/CPM groups were somnolence, dizziness, dry mouth dyspepsia, asthenia, and insomnia. A dose response effect was noted for somnolence, dizziness, dry mouth, asthenia, and insomnia for the IB/PSE/CPM high dose and IB/PSE/CPM low dose groups. Withdrawals due to AEs occurred most frequently in patients treated with IB/PSE/CPM high dose (2.2%), followed by PSE/CPM (1.8%), placebo (1.5%), and IB/PSE/CPM low dose (1.1%). There was a dose response effect noted for withdrawals due to somnolence.

In summary, this study supports the efficacy and safety of ibuprofen 200 mg/pseudoephedrine 30 mg/chlorpheniramine 2 mg in subjects with seasonal allergic rhinitis, and supports the contribution of ibuprofen to the efficacy of ibuprofen /pseudoephedrine/chlorpheniramine (IB/PSE/CPM). This review is not able to assess the contribution of CPM or PSE/CPM to the combination product because appropriate active controls needed to assess the contribution of PSE and CPM were not included in this study. The minimum effective dose of the product is IB 200 mg/30 mg PSE/2 mg CPM. This dose was statistically superior to placebo for relief of allergy symptoms and of allergy-associated headache, facial pain/pressure/discomfort. There is no added efficacy with IB 400 mg/ PSE 60 mg/CPM 4 mg and there is a dose-related increase in AEs with the higher dose. The study supports the sponsor's proposed dose of 1 tablet (IB 200 mg/PSE 30 mg/CPM 2 mg) every 4-6 hours.

3.1.2. Objective/Rationale

The objective of this study was to demonstrate the contribution of ibuprofen to the overall and analgesic effectiveness of IB/PSE/CPM in relieving the symptoms of SAR. The study was also to determine the minimum effective dose of the combination and the minimum effective dose of the antihistamine component of the combination [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-223].

3.1.3. Study design

This was a one-week, multi-center, multiple dose, double-blind, double-dummy, placebo-controlled, randomized, parallel-group, Phase 3 study. A minimum of 960 patients (approximately 240 in each of 4 study arms) were to complete the pain severity assessment after the first dose of study medication. A minimum of 880 patients (approximately 220 in each of 4 study arms) were to complete the entire one-week treatment period. A total of 1631 patients were screened and 1070 were enrolled and randomized to treatment at 49 study centers [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-80, 8-79-81, 8-79-223 to 8-79-226]. Patients had a 2-year history of SAR to an aeroallergen relevant to the spring allergy season. The first subject was enrolled on 2/13/01 and the last subject completed the study on 7/11/01 [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-3, 8-79-223 to 8-79-226].

An outline of the study design is presented in Table 3.1.1. At the screening visit, patients had informed consent, inclusion and exclusion criteria checked, skin tests (if not performed in the 2 years), history, and physical examination. Patients meeting inclusion and exclusion criteria were provided with a run-in diary and were instructed to assess the severity of their allergy symptoms each morning upon awakening and each evening prior to going to bed over the next 3 to 30 days. Patients returned to the study site when they experienced at least moderate allergy-associated headache and/or facial pain/pressure/discomfort and they had experienced allergy symptoms and assessed the severity of those symptoms for at least 3 consecutive days [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-33].

Patients meeting study inclusion/exclusion criteria at baseline were randomized to one of the four treatment groups and medications were dispensed in a double blind, double dummy fashion. Randomization was in a 1:1:1:1 ratio. The four treatment groups were [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-32 to 8-79-33]:

1. 2 tablets of IB 200 mg/PSE 30 mg/CPM 2 mg tablets (Active drug, high dose, Advil® Allergy Sinus)
2. 1 tablet of IB 200 mg/PSE 30 mg/CPM 2 mg tablet (Active drug, low dose, Advil® Allergy Sinus)
3. 1 tablet of PSE 30 mg/CPM 2 mg (Active control, Allerest® Maximum Strength)
4. 1 tablet of placebo

The active control PSE/CPM group (Allerest® Maximum Strength, with identifying markings removed) was included to assess the contribution of IB to the proposed combination product [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-36]. The sponsor did not provide information on the source of the active control PSE/CPM drug product, nor did they provide CMC information on its formulation. The sponsor did not state whether the active control PSE/CPM drug product is a currently marketed drug product.

Reviewer comment:
The sponsor's study was designed to assess the contribution of IB to the IB/PSE/CPM combination product, and so PSE/CPM is the appropriate active control. This study design is not able to assess the contribution of CPM, PSE, or PSE/CPM to the efficacy of the IB/SPE/CPM combination.

Allerest® Maximum Strength (30 mg PSE/2 mg CPM) was last listed in the 1997 PDR for Nonprescription Drugs[1] and has not been listed since then. A search of www.drugstore.com indicates that "Allerest" is not a listed product. It appears that this product is not currently marketed. More importantly, it is unclear if the active control product was a marketed product at the time of the study, and if so, it is also unclear if the product used in the study was the marketed product. It should also be noted that the recommended dosage for the Allerest® Maximum Strength product was 2 tablets (total dose 60 mg PSE/4mg CPM) every 4 to 6 hours, not to exceed 8 tablets in 24 hours (within the monograph-specified dosing). Even if the sponsor used marketed product for their active control, the dose of the active control was ½ that specified in the monograph, and efficacy cannot be assumed.

The dosing regimen is described below in more depth in the "Drug product and placebo" section of this review.

Subjects whose run-in scores did not meet severity criteria were given one additional opportunity to qualify for the study. These subjects were advised to continue to evaluate their allergy symptoms and return when: a) their allergy-associated pain worsened and/or b) their overall allergy symptoms worsened. These patients were to return to the site and qualify for dosing within 30 days of the screening visit, however [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-34].

The first dose of study medication was administered at the study site. Prior to dosing, patients provided a reflective assessment of their symptoms over the previous 12 hours. Patients were provided a diary and enough study medication for 7 days (20 more doses). Two and three hours after taking the dose of the study medication, patients provided an assessment of the severity of their allergy-associated headache and facial pain/pressure/discomfort. Patients were required to continue dosing approximately every 6 hours, up to 3 times daily for 19 to 20 more doses over the next 7 days, regardless of the presence or absence of symptoms. Prior to each dose of study medication, patients indicated whether they were experiencing an allergy-associated pain. Patients also provided reflective assessments of the severity of their allergy symptoms in the evening prior to bedtime and in the morning upon arising each day for the 7 day treatment period. Patients also provided an overall assessment of the study medication at the end of the Day 7 evening assessment [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-34, 8-79-35].

[1] PDR for Nonprescription Drugs, 18th edition, 1997, Medical Economics Co., Montvale, NJ, pages 702-703.

Patients recorded the following in their daily diary: pain severity at 2 and 3 hours after taking the first dose of study medication, presence of allergy-associated pain prior to each subsequent dose of study medication, reflective assessments of allergy symptoms at bedtime and upon arising, overall assessment of study medication, time of allergy symptom assessments, time of dosing, number of tablets taken, concomitant medication use, and adverse events. Patients brought their completed diary and unused medication to the study site at the end of their study visit. The diary card was reviewed by the study coordinator for accuracy and completeness and study medication accountability was performed [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-34, 8-79-35].

Pollen counts were obtained at a site from a validated pollen counting station within a 50-mile radius of each site. Pollen counts of the five most common allergens were obtained from the time that the first patient was enrolled into the study until the last patient completed the trial [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-267].

Table 3.1.1 Study outline, AD-99-02 [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-236]

Visit	Screening	Run-In (3-30 days)	Baseline (within 30 days of screening)	Days 1-7	Return Visit
Informed consent	X				
Check screening inclusion/exclusion criteria	X		X		
Skin test, if necessary	X				
Medical History	X				
Physical Exam	X				
Check concomitant therapies		X	X	X	X
Urine pregnancy test in women	X		X		
Dispense run-in diary	X				
Morning and evening reflective allergy symptom scores		X	X	X	
Instantaneous assessment of allergy-associated headache and/or facial discomfort			X	X	
Dispense medications and study diary			X		
Randomization			X		
Overall assessment of study medication				X	
Check adverse events				X	X

3.1.4. Inclusion criteria

Notable inclusion criteria are summarized below. These reflect changes made in a single protocol amendment [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-37-38, 8-79-299]:

1. Male or female subjects of any race, at least 12 years of age
2. History of SAR involving an of the following symptoms: runny nose, itchy/watery/red eyes, nasal congestion, sneezing, itchy nose/throat/palate, allergy-associated headache, facial pain/pressure/discomfort
3. History of experiencing at least moderate headache and/or facial pain/pressure/discomfort which worsens during allergy season and responds to treatment with OTC analgesics or who have never been treated with OTC analgesics
4. Positive skin test to an aeroallergen prevalent during the current allergy study season

Patients were to meet the minimum sign/symptom scores as noted below at the baseline visit [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-245 to 8-79-246]. Symptoms assessed by patients and symptom scales are discussed later in this review.

1. Score of at least "moderate" for baseline instantaneous allergy-associated and/or facial pain/pressure/discomfort
2. A sum of at least 48/108 for the previous six morning and evening reflective symptom score assessments completed during the run-in phase.

3.1.5. Exclusion criteria

Notable exclusion criteria are summarized below [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-247 to 8-79-249]:

1. Women who were pregnant or nursing
2. Women of child-bearing potential who were not practicing a medically acceptable method of contraception
3. Significant nasal anatomic deformities or polyps causing obstruction or patients who had more than two operations to remove polyps or repair nasal sinus/passages
4. Upper or lower respiratory tract infection within 14 days of screening
5. Persistently colored nasal discharge or diagnosis of acute or chronic sinusitis
6. History of rhinitis medicamentosa within 6 months of enrollment
7. Patients with asthma requiring corticosteroid (systemic, inhaled, or topical) or antileukotriene treatment
8. Subjects with a history of experiencing moderate to severe chronic tension headaches (>15/month) within 6 months of enrollment
9. Chronic NSAID therapy, defined as taking a daily (5 to 7 days per week) regimen of prescription NSAIDs or prescription doses of OTC NSAIDs. Aspirin therapy (up to 325 mg per day) for cardiac prophylaxis was to be permitted.
10. Patients who had taken any of the following medications within the corresponding washout period prior to taking the first dose of study medication

Medication	Washout period prior to baseline
Astemizole	90 days
Hydroxyzine, loratadine, fexofenadine, cetirizine	5 days
Other oral antihistamines, all forms	5 days
Topical azelastine	5 days
Ocular antihistamines	3 days
Leukotriene inhibitors	14 days
PSE	3 days
Herbal SAR medications	3 days
Intranasal saline	12 hours
Ocular NSAIDS	3 days
Oral immediate release analgesics	6 hours
Sodium naproxen	12 hours
Oral sustained release analgesics and COC-2 inhibitors	24 hours
Cromolyn sodium	14 days
Intranasal corticosteroids	14 days
Systemic, oral, inhaled, topical corticosteroids	30 days
Ocular corticosteroids	14 days
Topical ocular and nasal decongestants	24 hours

3.1.6. Protocol amendments

There was one protocol amendment, dated 1/16/01. The protocol amendment modified inclusion criteria to allow the participation of patients with a history of headache or facial pain/pressure/discomfort if they have never been treated with OTC analgesics. The protocol amendment also added an exclusion criterion for patients who had taken migraine preparations within the 8 hours prior to the first dose of study medication. The sponsor also made an administrative change to provide for time windows for the assessment of instantaneous pain intensity [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-218, 8-79-299 to 8-79-3003]. The sponsor states that these changes were made prior to breaking the blind for the study. The revisions were included in a background document for a Pre-NDA meeting on 11/29/01 with the Agency. These revisions were discussed at the meeting and were acceptable to the Agency [Meeting Minutes of 11/29/01, IND 61,725, N010, MR, 10/29/01].

3.1.7. Drug product and placebo

The sponsor provided double blind study medication packaged in blister packs. Lot numbers for study drug and placebo were as follows [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-52]:

Treatment Group	Lot Number
IB 400 mg /PSE 60 mg/CPM 4 mg	WH0899-0005-002
IB 200 mg/PSE 30 mg/CPM 2 mg	WH0899-0005-002
PSE 30/CPM 2 (Allerest® Maximum Strength, debossed)	WH0001-0019-002
Placebo-IB/PSE/CPM	WH0436-0113-001
Placebo-PSE/CPM	WH0436-0116-001

The clinical formulation of the active drug used in this study was qualitatively and quantitatively similar, but not identical to the to-be-marketed product [cmc/overview.pdf, page 4-13-2]. Active ingredients were identical in the product used in the study and the to-be-marketed product. There were small differences in inactive ingredients between the product used in the study and the to-be-marketed product. These are noted below in Table 3.1.2.

Table 3.1.2 Differences between the product used in this study and the to-be-marketed product [cmc/overview.pdf, page 4-13-2].

Inactive ingredient	WH-0899-0005 Study AD-99-02 mg/du	WH-0899-0006 NDA stability and to-be-marketed product, mg/du
Microcrystalline cellulose NF		
Microcrystalline cellulose NF		
Starch, pregelatinized NF		
Corn starch NF		

The sponsor provided double blind study medications for each of the following four treatment groups. These are summarized in Table 3.1.3.

Table 3.1.3. Double blind study medication [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-52, 8-79-249].

Treatment group Total dose	Dose per tablet	Number of active tablets	Number of placebo tablets to match active drug	Number of placebo tablets to match active control
IB/PSE/CPM	200 mg/30 mg/2 mg	2	0	1

Treatment group Total dose	Dose per tablet	Number of active tablets	Number of placebo tablets to match active drug	Number of placebo tablets to match active control
400 mg/60 mg/4 mg Active drug, high dose Advil® Allergy Sinus				
IB/PSE/CPM 200 mg/30 mg/2 mg Active drug, low dose Advil® Allergy Sinus	200 mg/30 mg/2 mg	1	1	1
PSE/CPM 30 mg/2 mg Active control Allerest® Maximum Strength	30 mg/2 mg	1	2	0
Placebo	0	0	2	1

Each patient was to take three tablets three times daily, morning, mid-day, and evening for the 7-day treatment period. Patients in the IB 400 mg/PSE 60 mg/CPM 4 mg group (active drug, high dose) were to take two tablets of active drug and one placebo tablet resembling the active control at each dosing time. Patients in the IB 200 mg/PSE 30 mg/CPM 2 mg group (active drug, low dose) were to take one tablet of active drug and one placebo tablet resembling the active drug and one placebo tablet resembling active control at each dosing time. Patients in the PSE 30 mg/CPM 2 mg group (active control) were to take two tablets to match the active drug and one tablet of the active control at each time of dosing. Patients in the placebo group were to take two tablets to match the active drug and one placebo tablet to match active control at each time of dosing. Dosing of study treatment is summarized in Table 3.1.4.

Table 3.1.4 Dosing of study treatment, active drug, active control, and placebo [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-250 to 8-79-251].

	Time of dose		
	Morning	Mid-day	Evening
Study arm			
IB/PSE/CPM 400/60/4 (active drug, high dose)	IB/PSE/CPM	IB/PSE/CPM	IB/PSE/CPM
	IB/PSE/CPM	IB/PSE/CPM	IB/PSE/CPM
	Pbo-PSE/CPM	Pbo-PSE/CPM	Pbo-PSE/CPM
IB/PSE/CPM 200/30/2 (active drug, low dose)	IB/PSE/CPM	IB/PSE/CPM	IB/PSE/CPM
	Pbo-IB/PSE/CPM	Pbo-IB/PSE/CPM	Pbo-IB/PSE/CPM
	Pbo-PSE/CPM	Pbo-PSE/CPM	Pbo-PSE/CPM
PSE/CPM 30/2 (active control)	Pbo-IB/PSE/CPM	Pbo-IB/PSE/CPM	Pbo-IB/PSE/CPM
	Pbo-IB/PSE/CPM	Pbo-IB/PSE/CPM	Pbo-IB/PSE/CPM
	PSE/CPM	PSE/CPM	PSE/CPM
Placebo	Pbo-IB/PSE/CPM	Pbo-IB/PSE/CPM	Pbo-IB/PSE/CPM
	Pbo-IB/PSE/CPM	Pbo-IB/PSE/CPM	Pbo-IB/PSE/CPM
	Pbo-PSE/CPM	Pbo-PSE/CPM	Pbo-PSE/CPM

Subjects were required to refrain from taking any of the medication listed under exclusion criteria during the study. Any concomitant medication used during the study was to be recorded in the subject diary.

The use of rescue medication was not permitted during the study. Subjects who took more than two doses of rescue medication (antihistamine, decongestant, analgesic) were to be discontinued [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-265]

Patient who missed more than 4 doses of medication throughout the study or missed 3 consecutive doses at any time were considered noncompliant and discontinued from the study. Compliance was assessed by review of the patients daily diaries and pill counts of used medication [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-261].

3.1.8. Assessment of symptoms

Patients assessed the severity of six individual allergy symptoms using a 4-point, 0-3 scale each evening prior to bedtime and each morning upon awakening. Assessments reflected the severity of symptoms over the preceding 12 hours. Patients assessed their symptoms twice daily as above during the 3 to 30 day run-in period, at baseline prior to taking the first dose of study medication, and twice daily as above during the 7-day treatment period [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-262].

The six individual allergic rhinitis symptoms assessed were:
1. Nasal congestion
2. Sneezing
3. Rhinorrhea (runny nose)
4. Itchy nose/throat/palate
5. Itchy/watery/red eyes
6. Headache, facial pain/pressure discomfort

The four point, 0-3 scale for assessment of allergic rhinitis symptom severity is displayed in Table 3.1.5.

Table 3.1. 5. Scale for assessment of allergic rhinitis symptom severity [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-262 to 8-79-263].

Score	Severity	Definition
0	Not present	No symptom is present
1	Mild	Symptom is present but with minimal awareness and is easily tolerated
2	Moderate	Symptom is definitely present and bothersome, but is tolerable
3	Severe	Symptom is hard to tolerate, may cause interference with daily activities and/or sleeping

At baseline, patients were to declare whether they were experiencing any pain with their allergy and if so, to declare whether they were having headache or facial pain/pressure/discomfort. Patients were required to have at least moderate allergy-associated pain at baseline to qualify to receive the first dose of study medication. They were to assess the severity of their pain on the scale displayed in Table 3.1.6. At 2 hours and 3 hours after taking the first dose of study medication, patients were asked to assess the severity of their allergy-associated pain using the same scale. Patients were provided with timers at the baseline visit to remind them to assess the severity of their pain at these times [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-264].

Table 3.1.6. Scale for assessment of allergy-associated pain severity [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-263].

Score	Severity
0	Not present
1	Mild
2	Moderate
3	Severe

Patients were also to record whether they were having pain associated with allergy prior to taking each dose of study medication during the 7-day treatment period [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-264].

Patients were also to rate the study medication as a treatment for their allergy symptoms using the 5-point, 0-4 scale displayed in Table 3.1.7.

Table 3.1.7. Scale for global assessment of study medication [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-263].

Score	Overall assessment
0	Poor
1	Fair
2	Good
3	Very good
4	Excellent

3.1.9. Variables

Various symptom scores were derived from the six individual reflective allergy symptom scores. These are described below [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-278 to 8-79-280]:

- Average daily individual reflective symptom score, derived by averaging the AM and PM values for each individual reflective symptom score
- Overall average individual reflective symptom score, derived by averaging the seven daily average individual symptom scores
- Total reflective symptom score (TSS), derived by summing the six individual reflective symptom scores
- Average total reflective symptom score (ATSS), derived by averaging the AM and PM TSS values for each day of the study
- Overall average total reflective symptom score (OATSS), derived by averaging the values for each of the seven ATSS
- AM overall total reflective symptom scores (AM OTSS), derived by averaging the seven AM TSS values
- PM overall total reflective symptom scores (PM OTSS), derived by averaging the seven PM TSS values

Various symptom scores were also derived from the individual scores for sneezing, itchy nose/throat/palate, and itchy/watery/eyes. These are described below [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-280]:

- Total reflective antihistamine symptom score (TASS), derived by summing the three individual reflective symptom scores
- Average total reflective antihistamine symptom score (ATASS), derived by averaging the AM and PM TASS values for each day of the study
- Overall average total antihistamine reflective symptom score (OATASS), derived by averaging the values for each of the seven ATASS scores

For each of the 6 qualifying morning and evening reflective assessment sets of symptom severity from the run-in phase and the reflective assessment set prior to dosing (if appropriate), a total reflective symptom score (TSS) was derived for qualification purposes by summing the individual reflective symptom scores among the six symptoms.

The baseline TSS was derived by averaging the sum of the six baseline values for each individual reflective symptom [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-66, 8-79-69].
Various pain intensity differences (PIDs) were derived from the Hour 2 and Hour 3 instantaneous allergy-associated pain scale assessments. PIDs were derived by subtracting the score at each post-dosing time point from the baseline pain score so that a higher value was indicative of greater improvement. The baseline pain score was defined as the instantaneous pain rating just prior to the first dose of study medication. SPID3 was defined as the time-weighted sum of the instantaneous pain intensity differences at two and three hours after the first dose of study medication [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-280 to 8-79-281].

3.1.9.1. Primary efficacy variable

The primary efficacy variable was the change from baseline in the overall average total reflective symptom score (OATSS). As noted previously, the six individual symptom scores used to calculate the OATSS were nasal congestion, sneezing, rhinorrhea (runny nose), itchy nose/throat/palate, itchy/watery/red eyes, and headache, facial pain/pressure discomfort. A TSS value was derived by averaging the values for the six individual symptoms at each of the two assessments each day. An average total reflective symptom score (ATSS), was derived by averaging the AM and PM TSS values for each day of the study. The overall average total reflective symptom score (OATSS), was derived by averaging the values for each of the seven ATSS. The baseline value was subtracted from the OATSS value to derive the change from baseline. The baseline TSS was derived by averaging the sum of the six baseline values for each individual reflective symptom[clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-65, 8-79-66, 8-79-69, 8-79-272, 8-79-276].

3.1.9.2. Secondary efficacy variables

Secondary efficacy variables include the following [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-65, 8-79-276]:

- Time-weighted sum of the instantaneous pain intensity difference scores at 2 and 3 hours after the first dose of study medication (SPID3)
- Change from baseline in the overall average reflective total antihistamine scores (sneezing, itchy/watery/red eyes, itchy nose, throat, palate - OATASS)
- Changes from baseline in the AM and PM overall total reflective symptom score (AM OTSS) and PM overall total reflective symptom score (PM OTSS)
- Incidence of pre-dose instantaneous allergy-associated pain (excluding the baseline measurement)
- Change from baseline in the average reflective total symptom score (ATSS) for each treatment day (Days 1-7)
- Change from baseline in the average reflective total antihistamine symptoms score for each treatment day (ATASS)
- Change from baseline in the overall average individual reflective symptom scores (except for pain)
- Change from baseline in the average individual reflective symptom scores for each treatment day (except for pain)

- The overall evaluation of study medication
- Onset of symptom relief

The sponsor defined onset of symptom relief as the first time point where a subjects experienced a ≥15% reduction from baseline in the TSS. For this analysis, two consecutive assessment time points were considered ½ day from one another in the time scale. If a subject never experienced a ≥15% reduction from baseline during the entire course of the study, time to onset was censored and assigned a score of 7 days [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-73 to 8-79-74, 8-79-268 to 8-79-272, 8-79-281].

Reviewer comment:
The sponsor chose many secondary endpoints. This document will review the following selected secondary endpoints:

- *Time-weighted sum of the instantaneous pain intensity difference scores at 2 and 3 hours after the first dose of study medication (SPID3)*
- *Change from baseline in the overall average reflective total antihistamine scores (sneezing, itchy/watery/red eyes, itchy nose, throat, palate - OATASS)*
- *Change from baseline in the average reflective total symptom score (ATSS) for each treatment day (Days 1-7)*
- *Change from baseline in the average reflective total antihistamine symptoms score (ATASS) for each treatment day (Days 1-7)*
- *Change from baseline in the overall average individual reflective symptom scores (except for pain)*
- *The overall evaluation of study medication*
- *Onset of symptom relief*
  - *The sponsor did not address durability of action in their definition of onset of symptom relief and therefore this endpoint will not support an onset of action claim*

3.1.9.3. Safety variables

Safety variables for this study included adverse events [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-79, 8-79-268 to 8-79-272].

3.1.10. Statistical Considerations

3.1.10.1. Analysis populations

The intent-to-treat group (ITT) was use for the analysis of efficacy. The ITT group was defined as those patients who provided a morning and evening reflective assessments of allergy symptoms for at least three consecutive days during the run-in phase, had a summed score of at least 48 out of 108 for the six twice daily qualifying evaluation sets of the reflective allergy symptoms, took at least one dose of double-blind study medication, and provided a reflective total symptom score for the evening of Study Day 1 or at least one reflective total symptom score from Days 2-7 [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-78].

A modified ITT group was used for the analysis of the SPID3. The modified ITT population was defined as those subjects who provided morning or evening reflective assessments of allergy symptoms for at least three consecutive days during the run-in phase and prior to dosing, had a summed score of at least 48 out of 108 for the six twice daily qualifying evaluation sets of the reflective allergy symptoms, provided a baseline assessment of allergy-associated pain that was at least moderate in severity, took at least one dose of double-blind study medication, and completed the two post-baseline assessments of allergy-associated pain at two and three hours after taking the first dose of study medication [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-78 to 8-79-79].

The sponsor also performed efficacy analyses on patients without major protocol violations (evaluable population) and on all randomized subjects. Safety analyses were based on all subjects who took at least one dose of double blind study medication [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-79].

3.1.10.2. Statistical analyses

All variables based on changes from baseline were analyzed using an ANOVA model including effect for treatment, corresponding baseline, and center. Allergy-associated pain was analyzed using a repeated measures logistic regression model with doses within subject as the repeated measure. Effects for treatment and baseline pain severity were included in the model. The overall evaluation of study medication scores was analyzed using the Cochran-Mantel-Haenszel test, controlling for center. [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-74 to 8-79-75].

The following objectives were considered of primary interest, in order of importance and of sequential analysis:

1. The efficacy of the 2 tablet dose of the IB/PSE/CPM combination
2. The efficacy of the 1 tablet dose of the IB/PSE/CPM combination
3. Comparison of efficacy of the 2 tablet and 1 tablet doses of the IB/PSE/CPM combination

To control for the Type I error rate, if an objective at any step was not achieved, the subsequent objectives were not eligible to be considered for significance . [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-75 to 8-79-76].

3.1.10.3. Statistical power

The sponsor calculated that approximately 240 patients per treatment group would be necessary to achieve 80% power to detect a 0.49 unit difference between IB/PSE/CPM and placebo for SPID3. This represents a 16.3% effect size, based on a maximum possible SPID3 of 3 units. The calculation assumed a SD of 1.9 units and a 0.05 level of significance and using a two-sided hypothesis test. The sponsor also estimated that this sample size would provide over 80% power to detect a treatment difference of 2.0 units in the OATSS between IB/PSE/CPM and placebo, assuming a SD of 7.5 units and a 0.05 level of significance. This represents an 11.1% effect size, based on a maximum possible

difference in OATSS of 18 units [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-75 to 8-79-76].

3.1.11. Results

3.1.11.1. Populations enrolled/analyzed

The protocol called for 960 evaluable patients with 240 in each treatment arm. A total of 1631 patients screened and 1070 were enrolled and randomized to treatment at 49 study centers. There were 1044 patients in the ITT group. Table 3.1.8 summarizes patient disposition [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-80, 8-79-81].

Table 3.1.8 AD-99-02, patient disposition [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-119].

	Total		Placebo		IB/PSE/CPM Low dose		IB/PSE/CPM High dose		PSE/CPM Active control	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomized	1070	(100)	265	(100)	263	(100)	269	(100)	273	(100)
Patients discontinued	113	(10.6)	28	(10.6)	27	(10.3)	30	(11.2)	28	(10 3)
Adverse event	18	(1.7)	4	(1.5)	3	(1 1)	6	(2 2)	5	(1 8)
Treatment failure	5	(0.5)	2	(0.8)	1	(0.4)	1	(0.4)	1	(0.4)
Protocol violation	84	(7.9)	22	(8 3)	20	(7 6)	21	(7.8)	21	(7.7)
Other	6	(0.6)	0	(0)	3	(1.1)	2	(0.7)	1	(0 4)
Patients in ITT population	1044	(97.6)	257	(97.0)	256	(97.3)	265	(98 5)	266	(97 4)
Patients in modified ITT population	1032	(96.4)	253	(95.5)	254	(96.6)	262	(97.4)	263	(96.3)
Patients in safety population	1070	(100)	265	(100)	263	(100)	269	(100)	273	(100)

There were 113 patients that discontinued from the study. Protocol violations were the most common reason for discontinuation. The proportion of patients discontinuing because of protocol violations was similar among the treatment groups. Discontinuations because of adverse events or other reasons were similarly distributed among the treatment groups.

Protocol deviations were common. Protocol deviations occurred in 37.3% of placebo patients, 37.6% if IB/PSE/CPM low dose patients, 31.5% if IB/PSE/CPM high dose patients, and 31.5% of PSE/CPM active control patients. The most common protocol deviations included missing assessment of the presence of allergy-associated pain or overall evaluation of study medication, missing dosing times or dosing amounts, and missing reflective allergy assessments. The types of proportion deviations occurred in were similarly distributed among treatment groups [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-83]. These data are summarized in Table 3.1.9.

Table 3.1.9 AD-99-02, protocol deviations [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-83].

Protocol deviation	Total N = 1070		Placebo N = 265		IB/PSE/CPM Low dose N = 263		IB/PSE/CPM High dose N = 269		PSE/CPM Active control N = 273	
	N	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Missing dosing times/amounts	108	(10.1)	33	(12.5)	26	(9.9)	25	(9.3)	24	(8.8)
Time point deviations	60	(5.6)	13	(4.9)	18	(6.8)	19	(7.1)	10	(3.7)
Missing pain presence/overall assessment	156	(14.6)	38	(14.3)	47	(17.9)	32	(11.9)	39	(14.3)
Assessment of pain > 5 minutes post-dose	54	(5.0)	10	(3.8)	13	(4.9)	13	(4.8)	18	(6.6)

Protocol deviation	Total N = 1070		Placebo N = 265		IB/PSE/CPM Low dose N = 263		IB/PSE/CPM High dose N = 269		PSE/CPM Active control N = 273	
	N	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Missing Day 1 reflective assessment	31	(2.9)	9	(3.4)	10	(3.8)	8	(3.0)	4	(1 5)
Missing Day 2-7 reflective assessment	83	(7.8)	17	(6.4)	24	(9.1)	23	(8 6)	19	(7 0)
Overall assessment >12 hours past last dose	52	(4.9)	17	(6.4)	10	(3.8)	12	(4 5)	13	(4 8)
Other	55	(5.1)	13	(4.9)	9	(3.4)	18	(6.7)	15	(5.5)

3.1.11.2. Baseline demographic and background characteristics

The population studied was largely of Caucasian race. There were more females than males in the study. The mean age was approximately 34.5 years in all treatment groups. Treatment groups were similar in gender and race [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-129]. These data are displayed in Table 3.1. 10.

Table 3.1.10 AD-99-02, demographics, ITT group [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-129].

Characteristic	Total N = 1045		Placebo N = 257		IB/PSE/CPM Low dose N = 256		IB/PSE/CPM High dose N = 265		PSE/CPM Active control N = 267	
Gender	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Male	300	(28.7)	72	(28.0)	71	(27.7)	79	(29.8)	78	(29 2)
Female	745	(71.3)	185	(72.0)	185	(72.3)	186	(70.2)	189	(70 8)
Race	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Caucasian	827	(79.1)	203	(79.0)	205	(80.1)	209	(78.9)	210	(78 7)
Black	112	(10.7)	31	(12.1)	24	(9.4)	26	(9.8)	31	(11 6)
Asian	10	(1 0)	4	(1.6)	1	(0 4)	3	(1 1)	2	(0 7)
Hispanic	79	(7.6)	17	(6.6)	19	(7.4)	24	(9.1)	19	(7.1)
Other	17	(1.6)	2	(0.8)	7	(2.7)	3	(1.1)	5	(1 9)
Age, years										
Mean age	34.5		34.1		34.6		34 5		34.8	
SD	13.5		13.3		13.7		13.2		13.7	
Range	12-85		12-81		12-70		12-75		12-85	

All patients had a history of SAR with an average duration of 17.6 years. Concomitant perennial allergic rhinitis was present in 67.8% of patients. Treatment groups were comparable for background history of allergic rhinitis [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-86, 8-79-137, 8-79-138].

3.1.11.3. Concomitant medications

Almost half of all patients (49.7%) took at least concomitant medication during the study. Psychotropics, H2 blockers/proton pump inhibitors/antacids, antihypertensives, and beta agonists were the most frequently taken medications of interest, used by 5.7%, 5.7%, 4.7%, 4.6% of the safety population, respectively. Concomitant antihistamines, decongestants, or combinations including antihistamines and/or decongestants were taken by 0.9% of patients, and were distributed similarly among treatment groups. Concomitant NSAIDs or analgesics were taken by 3.2% of patients, and were distributed fairly evenly