among the treatment groups [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-85, 8-79-135].

Reviewer comment:
It is unclear why the sponsor provided figures for use of concomitant medications in the safety population and not the ITT population. Overall, there was fairly infrequent use of concomitant medications that would interfere with assessment of efficacy, and use of these medications was fairly evenly distributed among the treatment groups. It is likely that use of concomitant medications had little effect on the assessment of efficacy.

3.1.11.4. Compliance

Most patients took 19 or more doses of study treatment. The average number of doses of study treatment was approximately 20. The treatment groups were comparable in the percent of doses of study treatment taken. The percentage of patients taking more than 19 doses of study medication was 97.7% in the placebo group, 97.3% in the IB/PSE/CPM low dose group, 98.1% in the IB/PSE/CPM high dose group, and 96.7% in the PSE/CPM active control group.

Reviewer comment:
Compliance appears to be adequate to allow for assessment of efficacy and safety, however compliance assessments based on patient reports may be unreliable.

3.1.11.5. Pollen counts

Pollen counts were to be 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 to be obtained from the time that the first patient was enrolled into the study until the last patient completes the trial [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-267]. The sponsor provided no analysis of pollen counts. No tabulations of pollen count data were provided.

Reviewer comment:
The sponsor should have provided this information. However, the study enrolled patients with springtime SAR by history and skin test, the study was conducted during the spring season, and patients were required to have moderate SAR symptoms to qualify for randomization to treatment. Lack of this information could disadvantage the sponsor if evidence for efficacy is borderline.

3.1.11.6. Efficacy variable outcomes

Efficacy was supported by primary and secondary variables as described below. Review of individual primary and secondary efficacy variables are found in the following sections. Changes from baseline were derived by subtracting the post-baseline value from the baseline value so that a higher value would be indicative of greater improvement [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-66].

Reviewer comment:
It appears that the sponsor has expressed the change from baseline as the absolute value so that changes are positive numbers. A higher value indicates a greater improvement.

3.1.11.6.1. Primary efficacy variable

The primary efficacy variable was the change from baseline in the overall average total reflective symptom score (OATSS) [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-65, 8-79-276]. Baseline TSS were similar among the treatment groups. The OATSS was greater for IB/PSE/CPM high dose, IB/PSE/CPM low dose, and PSE/CPM active control than for placebo. Effect sizes expressed as difference from placebo for the primary efficacy endpoint were 9.9%, 9.1%, and 4.3% for IB/PSE/CPM high dose, IB/PSE/CPM low dose, and PSE/CPM active control, respectively.

Table 3.1.11 Primary efficacy variable, overall average reflective total symptom score (OATSS) [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-141 to 8-79-143, 8-79-145].

	Placebo N = 257	IB/PSE/CPM Low dose N = 256	IB/PSE/CPM High dose N = 265	PSE/CPM Active control N = 267
Visit	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline TSS	12.13 (2 64)	12 31 (2.60)	12.19 (2 62)	12.23 (2 65)
Overall change from baseline, OATSS	3.80 (3.45)	5 43 (3.54)	5.59 (3 47)	4.57 (3.29)
Effect size*, %	0	9.1	9.9	4.3

*Effect size = (Overall change from baseline, OATSS active treatment minus Overall change from baseline, OATSS placebo) X 100
Maximum Score = 18

Both the IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose were statistically superior to placebo for the OATSS. The IB/PSE/CPM high dose was slightly more efficacious numerically, but not statistically, than the IB/PSE/CPM low dose (proposed dose). PSE/CPM active control was statistically superior to placebo. Both the IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose were statistically superior to IB/PSE.

Table 3.1.12 Pairwise comparisons, primary efficacy variable, overall average reflective total symptom score (OATSS) [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-146].

	IB/PSE/CPM High dose vs. Pbo	IB/PSE/CPM Low dose vs. PSE/CPM Active control	IB/PSE/CPM Low dose vs. Pbo	IB/PSE/CPM High dose vs. IB/PSE/CPM Low dose	PSE/CPM Active control vs. Pbo	IB/PSE/CPM High dose vs. PSE/CPM Active control
Difference	1.76	0.76	1.51	0.25	0.75	1.01
95% CI	(1.20, 2.32)	(0.21, 1.32)	(0.95, 2.07)	(-0.31, 0.81)	(0.19, 1.30)	(0.46, 1.57)
p value	<0.001	0.007	<0.001	0.376	0.009	<0.001

Reviewer comment:
These data provide convincing evidence of efficacy for both IB/PSE/CPM low dose (proposed dose) and IB/PSE/CPM high dose for the overall average reflective total symptom score, which reflects both allergic rhinitis symptoms as well as allergy-associated headache and/or facial discomfort.

IB/PSE/CPM at both doses were superior to PSE/CPM, which provides evidence supporting the contribution of IB to the efficacy of the IB/PSE/CPM combination product. As noted above, the overall average reflective total symptom score reflects both allergic rhinitis symptoms as well as allergy-associated headache and/or facial discomfort.

These data do not provide convincing evidence that IB/PSE/CPM high dose is more efficacious than IB/PSE/CPM low dose; both appear to be equally efficacious.

3.1.11.6.2. Secondary efficacy variables

3.1.11.6.2.1. SPID3

A key secondary efficacy variables 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 [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-276]. The SPID3 was greater for IB/PSE/CPM high dose and IB/PSE/CPM low dose than for placebo. The SPID3 for PSE/CPM active control and placebo were similar. 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. These data are displayed in Table 3.1.13.

Table 3.1.13 Secondary efficacy variable, instantaneous pain intensity difference scores [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-141 to 8-79-143, 8-79-145].

	Placebo N = 253		IB/PSE/CPM Low dose N = 254		IB/PSE/CPM High dose N = 262		PSE/CPM Active control N = 263	
Visit	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Baseline instantaneous allergy-associated pain severity	2 51	(0.50)	2 54	(0 50)	2.47	(0 50)	2 52	(0 50)
SPID3	2.01	(2 09)	2.81	(2.49)	2.80	(2.23)	2.10	(1 99)
Effect size*, %	0		26.7		26.3		3.0	

*Effect size = $\frac{\text{(SPID3 active drug minus SPID3 placebo) X 100}}{\text{Maximum Score = 3}}$

Both the IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose were statistically superior to placebo for the SPID3. The SPID3 for IB/PSE/CPM high dose and the IB/PSE/CPM were similar and not statistically significantly different from each other. The SPID3 for PSE/CPM active control was not statistically significantly different from placebo. Both the IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose were statistically superior to IB/PSE for the SPID3.

Table 3.1.14 Pairwise comparisons, secondary efficacy variable, instantaneous pain intensity difference scores [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-146].

	IB/PSE/CPM High dose vs. Pbo	IB/PSE/CPM Low dose vs. PSE/CPM Active control	IB/PSE/CPM Low dose vs. Pbo	IB/PSE/CPM High dose vs. IB/PSE/CPM Low dose	PSE/CPM Active control vs. Pbo	IB/PSE/CPM High dose vs. PSE/CPM Active control
Difference	0.86	0.65	0.75	0.11	0.10	0.76
95% CI	(0.50, 1.22)	(0.29, 1.01)	(0.39, 1.11)	(-0.25, 0.47)	(-0.26, 0.46)	(0.41, 1.11)
p value	<0.001	<0.001	<0.001	0.553	0.583	<0.001

Reviewer comment:
These data suggest that both IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose are efficacious for allergy-associated headache and/or facial discomfort, as measured by the SPID3 instrument.

IB/PSE/CPM at both doses were superior to PSE/CPM, which suggests that IB is contributing to the efficacy of the IB/PSE/CPM combination product for the treatment of allergy-associated headache and/or facial discomfort. It should be noted, however that there was no CMC information provided on the active control PSE/CPM product, and one may not firmly draw this conclusion.

Although the SPID3 was considered a secondary variable, it should be noted that the sample size for the study was calculated based on this variable. It may be more appropriate to consider this variable and the OATSS as a co-primary efficacy endpoints. It is important to note that these data provide evidence of efficacy for both allergy symptoms as well as allergy-associated headache and/or facial discomfort. These data provide support for the superiority of both IB/PSE/CPM doses over placebo and over active control for both allergic rhinitis symptoms and allergy-associated headache and/or facial discomfort. These data also provide evidence that suggests that IB contributes to the efficacy of the product for both allergic rhinitis symptoms and allergy-associated headache and/or facial discomfort.

These data do not provide convincing evidence that IB/PSE/CPM high dose is more efficacious than IB/PSE/CPM low dose; both appear to be equally efficacious.

3.1.11.6.2.2. OATASS

Another important secondary efficacy variable was the change from baseline in the overall average reflective total antihistamine score, OATASS [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-276]. The OATASS was composed of individual symptom scores for sneezing, itchy nose/throat/palate, and itchy/watery/eyes. The OATASS was greater for IB/PSE/CPM high dose and IB/PSE/CPM low dose than for PSE/CPM active control or placebo. The OATASS for PSE/CPM active control was greater than for placebo. Effect sizes expressed as difference from placebo for the OATASS were 10.6%, 9.8%, and 5.2% for IB/PSE/CPM

high dose, IB/PSE/CPM low dose, and PSE/CPM active control, respectively. These data are displayed in Table 3.1.15.

Table 3.1.15 Secondary efficacy variable, overall average reflective total antihistamine symptom score (OATASS) [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-141 to 8-79-143, 8-79-145].

	Placebo N = 257		IB/PSE/CPM Low dose N = 256		IB/PSE/CPM High dose N = 265		PSE/CPM Active control N = 266	
Visit	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Baseline TASS	5.65	(1.62)	5.77	(1.55)	5.67	(1.59)	5.74	(1.65)
Overall change from baseline, OATASS	1.92	(1.83)	2 80	(1.87)	2 87	(1.85)	2.39	(1 74)
Effect size*, %	0		9.8		10.6		5 2	

*Effect size = (OATASS active drug minus OATSS placebo) X 100
Maximum Score = 9

Both the IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose were statistically superior to placebo for the OATASS. The OATASS for IB/PSE/CPM high dose and the IB/PSE/CPM were similar and not statistically significantly different from each other. The OATASS for PSE/CPM active control was statistically superior to placebo. Both the IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose were statistically superior to IB/PSE for the OATASS.

Table 3.1.16 Pairwise comparisons, secondary efficacy variable, overall average reflective total antihistamine symptom score (OATASS) [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-146].

	IB/PSE/CPM High dose vs. Pbo	IB/PSE/CPM Low dose vs. PSE/CPM Active control	IB/PSE/CPM Low dose vs. Pbo	IB/PSE/CPM High dose vs. IB/PSE/CPM Low dose	PSE/CPM Active control vs. Pbo	IB/PSE/CPM High dose vs. PSE/CPM Active control
Difference	0.92	0.37	0.80	0.13	0.43	0 49
95% CI	(0 64, 1.21)	(0.08, 0.65)	(0.51, 1.09)	(-0.16, 0.41)	(0.14, 0.72)	(0.21, 0.78)
p value	<0.001	0.012	<0.001	0.390	0 003	<0 001

Reviewer comment:

These data provide convincing evidence of efficacy for both IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose for the overall average reflective total antihistamine symptom score, which reflects allergic rhinitis symptoms that would be expected to respond to an antihistamine—sneezing, itchy nose/throat/palate, and itchy/watery/eyes. It is interesting that both IB/PSE/CPM low dose (proposed dose, 2 mg CPM) and the IB/PSE high dose (4 mg CPM) were statistically superior to the PSE/CPM active control (2 mg CPM). This may indicate problems with the active control, which was used at a dose less than that of the monograph dose, may not have been a marketed product, and for which we have no CMC information. Although we have no prior information to suggest that the active control at this dose is efficacious, it was superior to placebo in this study.

It is also possible that the superiority of IB/PSE/CPM over PSE/CPM s may reflect some added benefit of IB in relief of non-pain-associated allergic rhinitis symptoms. Added benefit of IB may be coming from its prostaglandin synthetase inhibitor activity. Acular® (ketorolac tromethamine ophthalmic solution), is an NSAID ophthalmic solution that has demonstrated efficacy for treatment of seasonal allergic conjunctivitis and is approved for treatment of ocular itch associated with SAR.

The small difference in effect size for IB/PSE/CPM low dose (proposed dose) and the IB/PSE high dose indicates these doses may be on the high, flat end of the dose response curve for CPM.

These data do not provide convincing evidence that IB/PSE/CPM high dose is more efficacious than IB/PSE/CPM low dose; both appear to be equally efficacious.

3.1.11.6.2.3. Other secondary variables

Both IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose were superior to PSE/CPM active control and to placebo for change from baseline in the average reflective total symptom score (ATSS) for each day of treatment, Day 1 through Day 7. PSE/CPM active control was superior to placebo for change from baseline in the ATSS for each day of treatment, Day 1 through Day 7 [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-95].

Both IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose were superior to PSE/CPM active control and to placebo for change from baseline in the average reflective total antihistamine symptom score (ATASS) for each day of treatment, Day 1 through Day 7. PSE/CPM active control was superior to placebo for change from baseline in the ATASS for each day of treatment, Day 1 through Day 7 [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-95].

Both IB/PSE/CPM low dose (proposed dose) and the IB/PSE/CPM high dose were superior to PSE/CPM active control and to placebo for change from baseline in the each of the overall average individual reflective symptom scores (nasal congestion, sneezing, rhinorrhea, itchy nose/throat/palate, itchy/watery/red eyes). PSE/CPM active control was superior to placebo for change from baseline in the each of the overall average individual reflective symptom scores. The degree of effect for each individual symptom was similar within each treatment group; both active treatments and active control showed evidence of treatment effect for each individual symptom [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-96].

Overall evaluation of study medication by patients was "Good," "Very Good," or "Excellent" in 63%, 69%, 68%, and 43% for IB/PSE/CPM low dose (proposed dose), IB/PSE/CPM high dose, PSE/CPM, and placebo, respectively [clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-98, 8-79-143].

As noted previously, the sponsor did not address durability of action in their definition of onset of symptom relief. However, it is reasonable to note that IB/PSE/CPM low dose

(proposed dose), IB/PSE/CPM high dose, and PSE/CPM provided evidence of a treatment effect at the first time point after the first dose of study treatment (0.5 days). The protocol specified that time to onset was to be censored and a score of 7 days was to be assigned for subjects who never experienced a ≥15% reduction from baseline during the entire course of the study. There were 60 patients censored[clinstat\allergicrhinitis\ad9902\ad9902.pdf, pages 8-79-73 to 8-79-74, 8-79-98, crt\datasets\ad9902\efftran2.xpt].

Reviewer comment:
Secondary efficacy endpoints provide additional evidence for the efficacy of IB/PSE/CPM low dose and IB/PSE/CPM high dose, and for contribution of IB to the efficacy of the IB/PSE/CPM combinations. The sponsor's data provide evidence of some treatment effect as early as the first time point after the first dose of study medication, but the design of the study will not support an onset of action claim. These data do not provide convincing evidence that IB/PSE/CPM high dose is more efficacious than IB/PSE/CPM low dose; both appear to be equally efficacious.

3.1.11.6.3. Additional analyses

The sponsor conducted additional analyses of the primary and secondary efficacy endpoints using the per protocol population and using all randomized patients. The Agency also requested the sponsor to conduct analyses that treated patients who took prohibited medications as treatment failures and that used an alternative computation formula for SPID3 [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-104, 8-79-105].

Reviewer comment:
These additional analyses for the primary efficacy endpoint, for SPID3, and for OTASS were reviewed, and provided results that were consistent with the primary analysis.

3.1.11.7. Safety outcomes

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

3.1.11.7.1. Total drug exposure

Total exposure to study treatment may be estimated from compliance data. Most patients took 19 or more doses of study treatment. The percentage of patients taking more than 19 doses of study medication was 97.7% in the placebo group, 97.3% in the IB/PSE/CPM low dose group, 98.1% in the IB/PSE/CPM high dose group, and 96.7% in the PSE/CPM active control group.

Reviewer comment:
Compliance appears to be adequate to allow for assessment of safety.

3.1.11.7.4. Withdrawals due to AEs

There were 18 patients who withdrew from the study because of AEs. 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. There were 3 patients in the with IB/PSE/CPM high dose group (1.1%, 3/269), 2 patients in the PSE/CPM group (0.7%, 2/273), 0 patients in the IB/PSE/CPM low dose group (0%, 0/263), and 0 patients in the placebo group (0%, 0/265) who withdrew because of somnolence [clinstat\allergicrhinitis\ad9902\ad9902.pdf, page 8-79-107, 8-79-211 to 8-79-215].

Reviewer comment:
These data provide evidence for no new safety signal. There is a suggestion of a dose response effect for withdrawals overall. There is a clear dose response effect for withdrawals due to somnolence in the IB/PSE/CPM groups.

Reviewed by:

/S/

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

/S/

Mary Purucker, M.D., Ph.D.
Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Purucker/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/Barnes/CPMS
HFD-550/Fang/Medical Reviewer
HFD-550/Dean/CSO
HFD-560/Chang/Supervisory CSO

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/s/

Charles Lee
10/23/02 04:23:38 PM
MEDICAL OFFICER

Mary Purucker
10/23/02 04:57:30 PM
MEDICAL OFFICER
Concur. The data provided does not constitute substantial evidence of the efficacy of chlorpheniramine 2 mg administered alone.

Badrul Chowdhury
10/25/02 03:47:37 PM
MEDICAL OFFICER

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secret and/or

confidential

commercial

information

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:		**Phone:**	301-827-2090
Pages:	3 (including cover page)	**Date:**	23 October 2002
Re:	NDA 21-441CMC Comments		

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

- **Comments:**

Dear Dr. Kim,

Dr. Bhavnagri has asked that the following comments be conveyed to you for the above mentioned NDA. I hope you find these comments helpful. Feel free to call me if you have any questions at 301-827-2536.

Sincerely,

Jane A. Dean
Project Manager

CMC Information Requests for NDA 21-441

1. Please confirm that tests of identity for the three drug substances will be performed by Wyeth-Ayerst if the drug substances are received from the manufacturers with a certificate of analysis.

2. Please give explanations for superscripts A, B and C in the components and composition table on 4-15-3.

3. Please clarify the designation "mg/du" in the components and composition table on 415-3

4. Please give the function of each inactive ingredient in the components and composition table on 4-15-3.

5. Please indicate the number of caplets in a typical batch size and give the batch composition.

6. The limit of ——— for the weight of caplets in the "In-Process and Controls" table given on 4-15-208 is not clear. Please clarify this limit.

7. Please set a limit for total impurities.

8. Please describe any reprocessing operations that are undertaken during the manufacture of the drug product.

9. The component and composition table for the drug product ——— as an ingredient. Please indicate what role IPA plays in the manufacture of caplets.

10. Please give the specification for ——— of the pseudoephedrine hydrochloride content.

11. The analytical methods are submitted in one section of the NDA and the validation of the methods is given in a different section of the NDA. Only a partial validation is performed for the to-be-marketed formulation. The ranges used in the validation of the ——— methods are not the same. Linearity is established for a dynamic range of ——— of the nominal concentration whereas the range for accuracy and recovery is from ——— of the nominal concentration.

    Please perform a full validation on the formulation for which approval is sought, and submit the methods and the validation together in a single submission along with the other all the other information required for a methods validation package. This submission should be in triplicate.

12. Six months of stability data is not enough. The results were also very difficult to evaluate for the following reasons:

(a) The information presented seemed to be completely random

(b) The results of one storage condition were not clearly separated from the next storage condition

(c) The packaging code was given instead of giving a brief description of the container closure system e.g. pouch or blister

(d) The container evaluation parameters were separated from the assay values for the three drugs and degradants and the dissolution and dissolution profile values were again separated from the other results.

Please submit additional stability data. Please submit the information in the order in which the tests are listed on 4-15-320. Please give one table for each batch and container/closure system. Within each table organize the information in such a way that the results of each test can be compared at the various storage conditions.

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/s/

Jane Dean
10/31/02 04:03:46 PM
CSO

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: Ms. Filomena Gesek	**From:** Ms. Jane A. Dean, RN, MSN
Fax: 973-660-7187	**Fax:** 301-827-2531
Phone: 973-660-5825	**Phone:** 301-827-2090
Pages: 3 (including cover page)	**Date:** 7 October 2002
Re: NDA 21-441 Labeling Comments	

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

- **Comments:**

Dear Ms. Gesek,

Our labeling reviewers have the followingrecommendations:

I. Please inform the sponsor to further revise the carton, blister pack pouch, and pouch dispenser labels as follows:

A. Carton and Pouch Dispenser Labels

1. Principal Display Panel

a. Add "fever reducer" to the pharmacological category statement under the statement of identity for the analgesic

b. Remove ~~—~~ from phrase "Sinus ~~———~~ Pressure." in the promotional statement.

2. Side and Top Panels:

a. Change company name from [redacted] to "Wyeth Consumer" before the term "Healthcare."

b. Remove [redacted] from phrase "Sinus [redacted] Pressure" from all sizes.

3. Drug Facts Labeling

a. Purposes:

To the right of ibuprofen under Active ingredients, change [redacted] to "Pain reliever/fever reducer."

b. Uses:

(i) Remove [redacted] The indication is a more serious condition which may require medical attention, thus, is not appropriate for OTC use.

(ii) Add "common cold" after "temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies and."

(iii) Remove [redacted] from phrase "sinus [redacted] pressure."

(iv) Include "fever" as an additional bullet

c. Warnings:

Add "if you" to the subheading "Do not use."

Under that subheading, delete [redacted] from both clauses at the immediate right of the bullets.

Under "When using this product"

Add a 7th prebulleted statement "alcohol, sedatives, and tranquilizers may increase drowsiness."

Under "Stop use and ask a doctor if"

(i) Change [redacted] to "nasal congestion lasts for more than 7 days."

(ii) Change [redacted] to "fever lasts for more than 3 days."

(iii) Add as a 5th prebulleted statement "symptoms continue or get worse."

(iv) After "stomach pain occurs with use of this product," add "or if even mild symptoms persist."

d. Directions

For the direction "adults: take 1 caplet every 4-6 hours while symptoms occur," substitute [redacted] for "occur," and add a period followed by "If symptoms do not respond to 1 caplet, 2 caplets may be used."

e. Other information

Relocate "above" to precede 40°C.

B. Blister pack label:

Change company name from [redacted] to "Wyeth Consumer" before the term "Healthcare."

C. Pouch

a. Change Drug Facts labeling as in carton.

b. Change company name from [redacted] to "Wyeth Consumer Healthcare."

II. Inform the sponsor that the agency recommends the following:

A. inclusion of the established name "ibuprofen 200 mg, pseudoephedrine HCl 30 mg, chlorpheniramine maleate 2 mg coated tablets" on the Principal Display Panel of the carton and pouch dispenser labels.

B inclusion of subheading "Questions or comments?" a telephone number, and days and times of day of availability of someone to answer the telephone.

C. inclusion of "This package for household without young children." to be conspicuously labeled on the pouch dispenser.

I hope you find these comments helpful. 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
10/7/02 03:17:09 PM
CSO

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: Ms. Mary Davis	**From:** Ms. Jane A. Dean, RN, MSN
Fax: 973-660-7187	**Fax:** 301-827-2531
Phone: 973-660-5825	**Phone:** 301-827-2090
Pages: (including cover page) 2	**Date:** 13 August 2002
Re: NDA 21-441 BioPharm comments	

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

• **Comments:**

Dear Ms. Davis,

Our biopharm reviewer has the following comments:

1. At the present time, Wyeth has not submitted sufficient in vitro data to support their proposed specification of NLT —— in 45 minutes. Given that >99% of the ibuprofen, chlorpheniramine, and pseudoephedrine contained in this dosage form is dissolved in approximately 20 minutes, such a specification is neither discriminating nor necessary. Instead of the proposed specification, the Agency proposes the following: NLT —— dissolved at 20 minutes. Wyeth is asked to either accept this proposed revision to the in vitro dissolution, or to provide sufficient information (in both a tabular and graphical format) demonstrating the need for either their original proposed specification or an alternative.

2. In light of the finding that in the fed treatment, mean *Tmax values were increased (~1 hour) for pseudoephedrine and chlorpheniramine,* the applicant is suggested to address the effect of food on Tmax observed with *pseudoephedrine and chlorpheniramine* in Advil Allergy Sinus Caplets in their proposed labeling.

Sincerely,

Jane A. Dean, RN, MSN
Project Manager

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/s/

Jane Dean
8/13/02 12:32:52 PM
CSO

Dennis Bashaw
8/14/02 05:48:44 PM
BIOPHARMACEUTICS

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

REQUEST FOR CONSULTATION

TO (Division/Office)
ssociate Director, Medication Error Prevention
Office of Post Marketing Drug Risk Assessment, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM:
Ms. Jane A. Dean, RN, MSN x72536
Regulatory Health Project Manager

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
30 May 2001		21-441	NDA	28 February 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
ibuprofen 200 mg pseudoephedrine 30 mg chlorpheniramine 2 mg	Standard	Class 3	31 October 2002

NAME OF FIRM: Wyeth Healthcare Products

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER (SPECIFY BELOW). Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e g POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

PDUFA DATE: 28 December 2002
ATTACHMENTS: Last Approved Labeling Text, Current Labeling Text, Proposed labeling Text
CC: Fang, Christina; Katz, Linda
Archival NDA 21-441
HFD-550/Division File
HFD-550 /RPM
HFD-550/Reviewers and Team Leaders
HFD-560/Division File
HFD-560/RPM
HFD-560/Reviewers and Team Leaders

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Christina Fang, MD/Jane A. Dean, RN, MSN	☒ E-MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER Jane A. Dean, RN, MSN x72536

ast Approved Labeling Text

There is no last approved labeling text available since Advil® Allergy Sinus Caplets will be a new combination drug product. The proposed labeling for Advil® Allergy Sinus is based upon the following:

(1) Approved labeling for Advil® Cold & Sinus Caplets (NDA 19-771 – approved September 19, 1989 for ibuprofen 200 mg/pseudoephedrine 30 mg). The labeling for Advil Cold & Sinus is based in part upon the approved labeling for Advil® Tablets (NDA 18-989 – approved May 18, 1984 for ibuprofen 200 mg). In addition, labeling is based upon the approval letter dated May 23, 2001 for NDA 19-771/S-020 (Advil® Flu & Body Ache Caplets - ibuprofen 200 mg/pseudoephedrine 30 mg).

(2) Two Final Monographs contained in 21 CFR 341 "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use":

(a) Final Monograph for OTC Antihistamine Drug Products; Final Rule [57 FR 58356 (December 9, 1992)], and

(b) Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule [59 FR 43386 (August 23, 1994)].

Particular reference is made to 21 CFR 341.12 and 341.72, and 21 CFR 341.20 and 341.80.

(3) The "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use" Tentative Final Monograph for Combination Drug Products [21 CFR 341.40 and 341.85; 53 FR 30522 (August 12, 1988)].

(4) Study AD-99-02, which was conducted to support the efficacy and safety of the product.

Please refer to Item 3: Summary – Annotated LabelingVol. 9. pg. 9. and the Proposed Text Vol. 9. pg. 9..

Current Labeling Text

There is no current labeling text available since Advil® Allergy Sinus Caplets will be a new combination drug product. The proposed labeling for Advil® Allergy Sinus is based upon the following:

(5) Approved labeling for Advil® Cold & Sinus Caplets (NDA 19-771 – approved September 19, 1989 for ibuprofen 200 mg/pseudoephedrine 30 mg). The labeling for Advil Cold & Sinus is based in part upon the approved labeling for Advil® Tablets (NDA 18-989 – approved May 18, 1984 for ibuprofen 200 mg). In addition, labeling is based upon the approval letter dated May 23, 2001 for NDA 19-771/S-020 (Advil® Flu & Body Ache Caplets - ibuprofen 200 mg/pseudoephedrine 30 mg).

(6) Two Final Monographs contained in 21 CFR 341 "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use":

(a) Final Monograph for OTC Antihistamine Drug Products; Final Rule [57 FR 58356 (December 9, 1992)], and

(b) Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule [59 FR 43386 (August 23, 1994)].

Particular reference is made to 21 CFR 341.12 and 341.72, and 21 CFR 341.20 and 341.80.

(7) The "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use" Tentative Final Monograph for Combination Drug Products [21 CFR 341.40 and 341.85; 53 FR 30522 (August 12, 1988)].

(8) Study AD-99-02, which was conducted to support the efficacy and safety of the product.

Please refer to Item 3: Summary – Annotated LabelingVol. 9, pg. 9 and the Proposed Text Vol. 9, pg. 9.

Proposed Labeling Text

Whitehall-Robins is seeking approval to market a new combination drug product containing ibuprofen/pseudoephedrine/chlorpheniramine under the tradename Advil® Allergy Sinus Caplets. Note: many of the documents throughout this application refer to the product as Advil® Multi-Symptom Allergy Sinus, the originally proposed tradename.

The caplets will be packaged in blisters (the inner container) inside cartons (the outer container), with 10 caplets per blister card. Whitehall-Robins plans to market a 10, 20 and 40-count size, containing one, two and four blister cards, respectively. In addition, we plan to sample a 1-count size to physicians. A single caplet will be packaged in a pouch, and the pouches will be packed in dispensers (50 pouches per dispenser).

The labeling of the outer containers for the consumer sizes will be "Drug Facts" compliant. The "Drug Facts" information is listed below. Also provided below is the proposed text for the other panels of the cartons, such as the principal display panel (PDP), and other packaging components such as the back of the blister card.

Please note that the proposed text provided below is for content only. Since the information contained on each of the sizes is the same, we are providing proposed text for a "representative size" of the outer container. Due to the difference in the sizes of the cartons, the layout of the information will differ among the carton sizes. Please refer to the individual PDF files of the carton, blister back, dispenser, and pouch for the exact layout and format of the labeling. However, it is noted that the dimensions of the outer carton for the 10 and 20-count are identical. Therefore, the content and format for these two sizes will be exactly the same, except for the numerical count on the PDP. The 10-count will state "10 Coated Caplets" and the 20-count will state "20 Coated Caplets". This will be the only difference between these two sizes.

In addition to the files, "mock-ups" are provided. Wherever "Drug Facts" information is required to conform to the formatting per 21 CFR 201.66, the formatting and type sizes of the various "Drug Facts" information items, such as title, headings, bullets, spacing, etc., will be located on the reader for that particular component. This information is contained within a table entitled "LEGAL TEXT DEFINED". For labeling components that do not need to comply with 21 CFR 201.66, *e.g.*, inner container labels, PDP, and the professional sample pouches, etc., the type sizes will be listed as "N/A" in the table.

The professional samples, the pouch and dispenser, will contain the following statement: "FOR PROFESSIONAL USE ONLY – Not for Retail Sale". Per the "Drug Facts" Final Rule, 21 CFR 201.66, professional samples do not need to be "Drug Facts" compliant. However, since there is sufficient space on the dispenser to accommodate the "Drug Facts" format, the labeling on the dispenser will comply with 21 CFR 201.66. Due to the relatively small size of the pouches, some of the required "Drug Facts" information will be included in the labeling, but will not be in the "Drug Facts" format. Please refer to the PDF file and mock-up of the pouch for the content and format of the labeling on this component.

5 pages redacted from this section of the approval package consisted of draft labeling

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/s/

Christina Fang
6/3/02 11:48:35 AM

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

REQUEST FOR CONSULTATION

(Division/Office):
Dr. Viswanathan
Division of Scientific Investigations
HFD-48, MPN 1
7520 Standish Pl., Rm. 151

FROM:
Dr. Christina Fang/Jane A. Dean, RN, MSN x72536
DAAODP, HFD-550

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2 August 2002		**21-441**	**NDA original submsiion**	**28 February 2002**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Advil Allergy Sinus (ibuprofen/pseudoephedrine/chlorpheniramine)	**Standard**	**3S**	**30 September 2002**

NAME OF FIRM: **Wyeth Healthcare Products**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL:	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Per Dr. Fang's request, please inspect the following clinical site:**

For Study # AD-99-01 (A Single Dose, Randomized, Open-Label, Four-Way Crossover Pharmacokinetic Interaction Study of Advil Multi-Symptom Allergy Sinus):

[ ]

If you need any additional information, please contact the Project Manager, Jane A. Dean, RN, MSN at x 72536. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Christina Fang/Jane A. Dean, RN, MSN x72536	☐ E-MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jane Dean
8/2/02 01:26:05 PM

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confidential

commercial

information

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

(Division/Office):	FROM:
Robert Shibuya/Karen Storms Division of Scientific Investigations HFD-45, MPN 1 7520 Standish Pl., Rm. 125	Dr. Christina Fang/Jane A. Dean, RN, MSN x72536 DAAODP, HFD-550

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1 August 2002		21-441	NDA original submsiion	28 February 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Advil Allergy Sinus (ibuprofen/pseudoephedrine/chlorpheniramine)	Standard	3S	30 September 2002

NAME OF FIRM: Wyeth Healthcare Products

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☒ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Per Dr. Fang's request, please inspect the following clinical sites:**

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

If you need any additional information, please contact the Project Manager, Jane A. Dean, RN, MSN at x 72536. Thank you.

NATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Christina Fang/Jane A. Dean, RN, MSN x72536	☒ E-MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jane Dean
8/1/02 04:06:07 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: June 20, 2002

To: Mary Davis	**From:** Carmen DeBellas
Company: Wyeth Healthcare	Division of Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Fax number: 973-660-7187	**Fax number: 301-827-2531**
Phone number: 973-660-5825	**Phone number:** 301-827-2090

Subject: Information Request from Biopharm Reviewer for NDA 21-441 Advil Allergy Sinus Caplet

Total no. of pages including cover: 1

Comments:

Please ask to sponsor to address the following issue:

PK Comments:

In PK studies AD-99-01 and AD-99-03, the Tmax values reported by the sponsor for ibuprofen do not seem right. Looking at the ibuprofen profiles in both studies, Tmax appears to be around — hours rather than around 1.7 hrs reported by the sponsor. Due to appearance of double peaks for ibuprofen in both studies, it is assumed that the computer picked Tmax value based on the first peak.

In light of that, the sponsor is suggested to look at data for the other components as that may also change some of the findings (e.g, food effect on pseudoephedrine, gender effect etc) they have reported in the submission.

Document to be mailed: ☐ **YES** ☑ **NO**

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/s/

Carmen DeBellas
6/20/02 11:39:13 AM
CSO

Carmen DeBellas
6/20/02 11:41:44 AM
CSO

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: June 3, 2002	DUE DATE: November 8, 2002	ODS CONSULT #: 02-0129

TO: Lee Simon, M.D.
Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products
HFD-550

THROUGH: Jane A. Dean, RN
Project Manager
HFD-550

PRODUCT NAME:	NDA SPONSOR:
Advil Allergy Sinus (Chlorpheniramine Maleate, Ibuprofen, and Pseudoephedrine Hydrochloride Tablets) 2 mg 200 mg 30 mg NDA#: 21-441	Wyeth Healthcare Products

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Advil Allergy Sinus" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objections to the use of the proprietary name, Advil Allergy Sinus. However, DMETS recommends implementing the labeling revisions outlined in Section III of this review, in order to minimize potential errors with the use of this product.

This name, along with its associated labels and labeling, must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

/S/

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Room 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 8, 2002

NDA#: 21-441

NAME OF DRUG: Advil Allergy Sinus
(Chlorpheniramine Maleate, Ibuprofen, and Pseudoephedrine Tablets)
2 mg/200 mg/30 mg

NDA HOLDER: Wyeth Healthcare Products

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550), for assessment of the tradename "Advil Allergy Sinus" regarding potential name confusion with other proprietary and established drug names. Wyeth Healthcare Products currently markets several products using the root, Advil. Table 1 below lists the proprietary name and active ingredients of each of these products.

Table 1

Products	*Strength and Active Ingredient(s)*
Advil Tablets, Caplets, Gelcaps, LiquiGels	200 mg Ibuprofen
Advil Migraine LiquiGels	200 mg Ibuprofen
Advil Cold and Sinus	200 mg Ibuprofen and 30 mg Pseudoephedrine
Advil Flu and Body	200 mg Ibuprofen and 30 mg Pseudoephedrine
Childrens Advil Suspension	100 mg Ibuprofen per 5 mL
Junior Strength Advil Chewables	100 mg Ibuprofen
Childrens Advil Chewables	50 mg Ibuprofen
Childrens Advil Drops	50 mg Ibuprofen per 1.25 mL

PRODUCT INFORMATION

Advil Allergy Sinus is a combination product containing chlorpheniramine maleate 2 mg, ibuprofen 200 mg and pseudoephedrine hydrochloride 30 mg per tablet. The product is indicated to

The symptoms include: runny nose, sneezing, headache, itchy and/or watery eyes, itching of the nose or throat, minor aches and pains, nasal congestion, and sinus _ pressure. The dose and administration schedule of Advil Allergy Sinus for adults is one tablet every four to six hours while symptoms occur. Patients should not take more than six tablets within a 24-hour period. Physicians should be contacted for the dosing of children under 12 years of age. Advil Allergy Sinus will be packaged in blisters containing 10, 20, and 40 tablets.

II. RISK ASSESSMENT:

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name "Advil" has been utilized in the U.S. marketplace since 1984. A search was conducted of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to Advil Allergy Sinus to a degree where potential confusion between drug names could occur under the usual clinical practice settings. Searches of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. Since the proprietary name Advil has been in the U.S. marketplace for more than fifteen years, the standard DMETS prescription analysis studies were not conducted. However, the FDA Adverse Event Reporting System (AERS) was searched for any postmarketing safety reports of medication errors associated with the name Advil. The Drug Quality Reporting System (DQRS) was also searched for reports associated with any Advil product.

A. REFERENCE SEARCH

The search of the reference texts and databases did not identify any sound-alike or look-alike names of concern. However, as noted in Table 1 eight products are currently marketed which contain the root name 'Advil' in the proprietary name.

DDMAC did not have concerns about the name Advil Allergy Sinus with regard to promotional claims.

B. AERS DATABASE SEARCHES

The Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports of medication errors associated with any Advil product. The MEDDRA Preferred Term (PT) "Medication Error" and the terms "Advil" and "Adv%" were used as search criteria. The search identified one-hundred seventeen reports, however none of the reports involved name confusion within the Advil product line or between Advil and other products.

The Drug Quality Reporting System (DQRS) was also searched for reports associated with Advil. The DQRS search identified 68 reports, however none of the reports identified any cases of name confusion between the currently marketed Advil products or between Advil and other products.

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

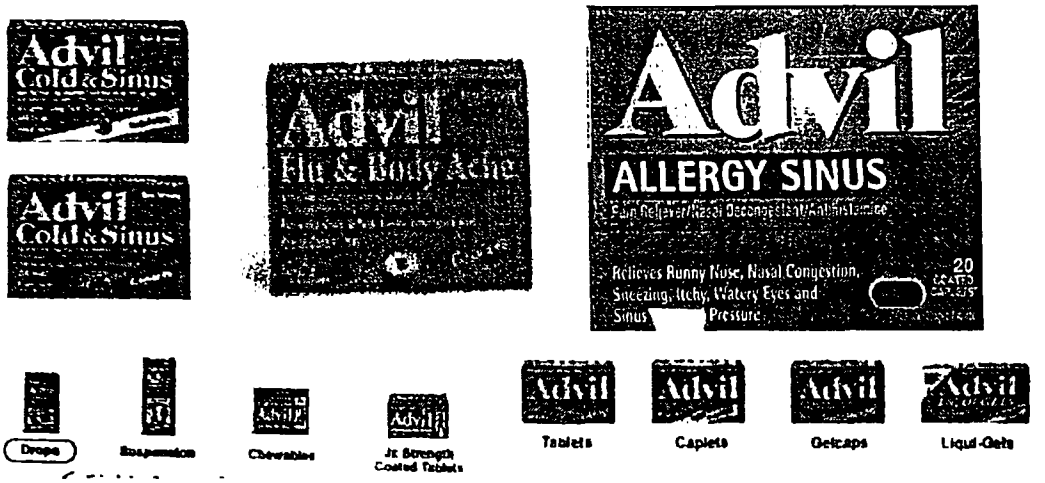
[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

C. SAFETY EVALUATOR RISK ASSESSMENT

A search of the AERS and DQRS databases did not identify any medication error reports involving name or product confusion with Advil. The overall number of medication error reports received by the Agency that are associated with over-the-counter products is low. Thus the fact that the searches did not identify any Advil cases is not unusual. Even though, DMETS has not identified any cases of medication errors, we will continue to monitor Advil medication error reports.

There are eight products currently in the market utilizing the root name Advil. All of which contain ibuprofen as an active ingredient and are used for pain relief and as an anti-pyretic. Two of the eight products contain pseudoephedrine as an additional ingredient and are also used to relieve nasal congestion. The proposed product, Advil Allergy Sinus, will be the first in this product line to contain three ingredients (i.e., ibuprofen, pseudoephedrine, and chlorpheniramine). Potential name confusion may occur between the existing multi-ingredient products Advil Cold & Sinus and Advil Flu & Body and the proposed product Advil Allergy Sinus because they all contain multiple ingredients and there is an overlapp of ingredients among the products. Additionally, potential name confusion is more likely with Advil Cold & Sinus and Advil Allergy Sinus since both names are similar except for the words 'Cold' and 'Allergy.' This is a similar nomenclature practice with other OTC products. If a patient took Advil Cold & Sinus in lieu of Advil Allergy Sinus, they should not experience any unexpected adverse events since Advil Cold & Sinus contains two of the ingredients found in Advil Allergy Sinus. In contrast patients who take Advil Allergy Sinus in lieu of Advil Cold & Sinus or Advil Flu & Body may experience adverse events associated with the antihistamine chlorpheniramine (e.g., drowsiness, dry mouth, thick bronchial secretions, or hypotension). Patients should ask their doctor if they have 'glaucoma' or a 'breathing problem such as emphysema or chronic bronchitis' prior to using Advil Allergy Sinus. This is not a warning for either Advil Cold & Sinus or Advil Flu & Body. DMETS notes that the potential for confusion exists between the multi-ingredient Advil products; however, all of the Advil products contain the appropriately displayed statement of identify which should help patients distinguish between the products. Moreover, the various products are packaged in different colors to help distinguish them (see below).



Drops Suspension Chewables Jr. Strength Coated Tablets Tablets Caplets Gelcaps Liqui-Gels

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Advil Allergy Sinus, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. CARTON LABELING

1. The statement of identity should be increased to a size that is reasonably related to the proprietary name and should contain the established name of the drug in accordance with CFR 201.61. Revise accordingly.

2. The statement of identity for Advil Allergy Sinus is 'Pain Reliever/Nasal Decongestant/Antihistamine.' However, the active ingredients are listed in the following order: Chlorpheniramine/Ibuprofen/Pseudoephedrine. The current presentation of the active ingredients does not allow the user to correlate the statement of identity to its respective ingredient (e.g., Pain Reliever—Ibuprofen) and may be confusing or misleading to the user. We recommend that the active ingredients correlate with the position and order of the statement of identity.

C. SINUS POUCH – Professional Sample

1. See Comment A1.

2. See Comment A2.

D. CONTAINER LABEL – Blister Pack

Include the dosage form "Tablet" after the active ingredients (i.e., ibuprofen 200 mg/pseudoephedrine 30 mg/chlorpheniramine 2 mg Tablet).

E. DISPENSER – Professional Sample

1. See Comment A1.

2. See Comment A2.

V. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Advil Allergy Sinus.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

B. DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Alina Mahmud
11/8/02 12:12:26 PM
PHARMACIST

Carol Holquist
11/8/02 02:17:26 PM
PHARMACIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

(Division/Office): ulmonary, HFD-570	FROM: **Jane A. Dean, RN, MSN** **DAAODP, HFD-550**

DATE **22 April 2002**	IND NO.	NDA NO. **21-441**	TYPE OF DOCUMENT **NDA**	DATE OF DOCUMENT **1 March 2002**

NAME OF DRUG **Ibuprofen 200mg/Pseudoephedrine 30mg/Chlorpheniramine 2mg**	PRIORITY CONSIDERATION **Standard**	CLASSIFICATION OF DRUG **Analgesic/Nasal decongestant/Antihistamine**	DESIRED COMPLETION DATE **1 September 2002**

NAME OF FIRM: **Wyeth Healthcare Products**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ■ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*.

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the efficacy and safety Study AD-99-02 with respect to the effect of pseudoephedrine and chlorpheniramine on allergy symptoms with emphasis on the contributing effect of chlorpheniramine 2mg. Please contact Jane A. Dean, RN, MSN, Project Manager, at x72536 if there are any questions. Thank you.

When you have finished the final review, please CC the review to Dr. Christina Fang and Jane A. Dean.

SIGNATURE OF REQUESTER **Christina Fang, MD/Jane A. Dean, RN, MSN**	METHOD OF DELIVERY (Check one) ☐ EMAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER **Jane A. Dean, RN, MSN**

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/s/

Christina Fang
4/23/02 04:20:34 PM

Division of OTC Drug Products Labeling Review

NDA 21-441

Submission Date: February 28, 2002
April 22, 2002
Review Date: September 30, 2002

Applicant: Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Applicant's Representative: Mary H. Davis
Director, Regulatory Affairs
973-660-5825

Drug: Advil® Allergy Sinus Coated Caplets
(ibuprofen 200 mg/
pseudoephedrine hydrochloride 30 mg/
chlorpheniramine maleate 2 mg tablet)

Pharmacologic Category: pain reliever/fever reducer/nasal decongestant/ antihistamine

Submitted: Carton Labels
10 caplets
20 caplets
40 caplets
Blister Pack Labels for 10's
Pouch and Dispenser Label for Professional Use Only

Background:

Ibuprofen is included as a single ingredient pain reliever/fever reducer in the tentative final monograph (TFM) for OTC analgesic, antipyretic, and antirheumatic drug products. Ibuprofen 200 mg is also approved in combination with pseudoephedrine HCl 30 mg in numerous NDA OTC products. The TFM for cough/cold drug products proposes to allow the combination of an analgesic, nasal decongestant, and antihistamine. There are numerous such products currently marketed OTC. Two approved under the NDA process are NDA 21-082 for Tavist® Allergy/Sinus/Headache containing clemastine fumarate 335 mg, acetaminophen 500 mg, and pseudoephedrine HCl 30 mg, and NDA 19-453 for Drixoral Plus® containing dexbrompheniramine maleate 3 mg, acetaminophen 500 mg, and pseudoephedrine sulfate 60 mg.

Reviewer Comment: Reviewer recommended additions are identified by red shaded text and deletions are identified by "strike out."

I. All Sizes (Cartons & Pouch Dispenser)

A. Principal Display Panel (PDP)

Advil®

ALLERGY SINUS

Pain Reliever/Fever Reducer/Nasal Decongestant/Antihistamine

Reviewer's comment: Statement of identity requirements under 21 CFR 201.61 are met with a description of the pharmacologic categories. We recommend the use of "ibuprofen 200 mg, pseudoephedrine HCl 30 mg, chlorpheniramine maleate 2 mg tablets" as the established name. Since an ibuprofen purpose is to act as a fever reducer, we recommend that this indication be added to the pharmacological category phrase for the ibuprofen.

Relieves Runny Nose, Nasal Congestion, Sneezing, Itchy Watery Eyes, and Sinus ——— Pressure

ADVIL ALLERGY SINUS (on image of caplet)

Qty. COATED CAPLETS*

*Capsule-Shaped Tablets

Reviewer's comment: Removal of — from this promotional statement is necessary. — may indicate a more serious condition than what the product is intended to relieve.

B. Drug Facts Panel

Drug Facts

Active ingredients (in each caplet)	*Purposes*
Chlorpheniramine maleate 2 mg	Antihistamine
Ibuprofen 200 mg	Pain reliever/fever reducer

Reviewer's comment: The purpose needs to be included.

Pseudoephedrine HCl 30 mg ..... Nasal decongestant

Uses

- temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies, and ——— common cold:

Reviewer's comment: ——— is a condition which may require medical intervention, and thus is not an appropriate OTC indication. "Common cold" is added to be consistent with uses of active ingredients in the same pharmacological categories in other products.

- runny nose
- itchy, watery eyes
- nasal congestion
- sneezing
- itching of the nose or throat
- sinus ——— pressure
- headache
- minor aches and pains
- fever

Reviewer's comment: same comment as in I.A above for ——— should also be listed to be consistent with the pharmacological category and with a warning below under the subheading "Stop use and ask a doctor" if fever lasts for more than 3 days.

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction which may include:

- hives
- facial swelling
- asthma (wheezing)
- shock

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

Do not use if you

- ——— have ever had an allergic reaction to any other pain reliever/fever reducer
- ———are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Reviewer's comment: Labeling more efficient with ——— ' in heading to avoid repetition in individual statements

Ask a doctor before use if you have

- ———
- a breathing problem such as emphysema or chronic bronchitis
- heart disease
- high blood pressure
- thyroid disease
- diabetes
- glaucoma
- ———
- trouble urinating due to an enhlarged prostate gland

Reviewer's comment: Moved last statement to first position for greater emphasis

Ask a doctor or pharmacist before use if you are

- [redacted]
- taking sedatives or tranquilizers
- [redacted]

[redacted]

When using this product

- **do not use more than directed**
- avoid alcoholic drinks
- be careful when driving a motor vehicle or operating machinery
- drowsiness may occur
- [redacted]
- take with food or milk if stomach upset occurs
- alcohol, sedatives and tranquilizers may increase drowsiness

Reviewer's comment: required statement under 21 CFR 341.72(c)(3) of the antihistamine monograph.

Stop use and ask a doctor if

- an allergic reaction occurs. Seek medical help right away.
- [redacted] nasal congestion lasts for more than 7 days

Reviewer's comment: The nasal decongestant monograph includes a 7 day maximum use limit for pseudoephedrine HCl.

- [redacted] fever ~~—~~ lasts for more than 3 days

Reviewer's comment: Stricken part is included in separate statement below. Added "for" to be consistent with other 7-day statement.

- you get nervous, dizzy, or sleepless
- symptoms continue or get worse
- stomach pain occurs with the use of this product or if even mild [redacted] persist

Reviewer's comment: both added phrases are used in labeling for ibuprofen/pseudoephedrine HCl in NDA 19-899.

- new or unexpected symptoms occur

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use [redacted] during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- adults: take 1 caplet every 4-6 hours while symptoms ——persist. If symptoms do not respond to 1 caplet, 2 caplets may be used.

  Reviewer's comment: "Persist" is a more precise term. Added sentence is included to be consistent with directions for the same active ingredients in the product category.
- do not take more than 6 caplets in any 24-hour period, unless directed by a doctor
- children under 12 years of age: consult a doctor

Other information

- read all warnings and directions before use. Keep carton.
- store in a dry place 20-25°C (68-77°F)
- avoid excessive heat above 40°C ——— 104°F)

  Reviewer's comment: Moved ——— to make statement clearer.

Inactive ingredients

carnauba wax, croscarmellose sodium, FD&C red no. 40 aluminum lake, FD&C yellow no. 6 aluminum lake, glyceryl behenate, hypromellose, iron oxide black, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, propylene glycol, silicon dioxide, starch, titanium dioxide

Questions or comments? Call 1-800-XXX-XXXX: [insert appropriate times when the phone will be answered by a person, e.g., weekdays 8AM to 11 PM EST; weekends 9 AM to 11 PM EST]

Reviewer's comment: We recommend that the heading, a telephone number, and days and times when someone is available to answer questions be added.

Reviewer's comment: Specifications provided are in compliance with 21 CFR 201.66(d).

C. Side or Top Panels

Advil® ALLERGY SINUS
or
Advil® ALLERGY
SINUS

APPEARS THIS WAY
ON ORIGINAL

Product inside sealed in plastic blister with foil backing. Do Not Use if plastic blister or foil barrier is broken.

——— Wyeth Consumer Healthcare
Madison, NJ 07940 Made in U.S.A.

Reviewer's comment: new company name
U.S. Patent Nos. 4,619,934 and 5,025,019
Appearance of the orange Advil® Allergy Sinus
caplet is a trademark of [redacted] Wyeth Consumer Healthcare
Reviewer's comment: new company name
UPC Code
Lot No. Exp. (in unvarnished area)

The 40-count size may also contain the following:

Relieves Runny Nose,
Nasal Congestion, Sneezing,
Itchy Watery Eyes, and
Sinus [redacted] Pressure
Reviewer's comment: same comment as in IA above.

II Pouch Dispenser

"This package for household without young children" is encouraged to be conspicuously labeled on the dispenser.
Reviewer's comment: per 16 CFR § 1700.5. The individual pouch packs are not child resistant.

III. Blister pack labels

Advil®
ALLERGY SINUS
IBUPROFEN 200 mg/PSEUDOEPHEDRINE HCl 30 mg/
CHLORPHENIRAMINE MALEATE 2 mg Tablets
ALLERGY ALERT AND
ALCOHOL WARNING.
READ CARTON BEFORE USE.
[redacted] Wyeth Consumer Healthcare, Madison, NJ 07940
Reviewer's comment: new company name
Lot:
EXP: PEEL & PUSH

IV. Pouch – One caplet

Reviewer's comment: Labeling needs same revisions as in Carton "Drug Facts." The new corporate name Wyeth Consumer Healthcare needs to be substituted for [redacted]

Recommendations:

I. This application is not approvable. Inform the sponsor to further revise the carton, blister pack pouch, and pouch dispenser labels as follows:

A. Carton and Pouch Dispenser Labels

1. Principal Display Panel

a. Add "fever reducer" to the pharmacological category statement under the statement of identity for the analgesic

b. Remove ——— from phrase "Sinus ——— Pressure." in the promotional statement.

2. Side and Top Panels:

a. Change company name from ' ——————— ' to "Wyeth Consumer" before the term "Healthcare."

b. Remove ——— from phrase "Sinus ——— Pressure" from all sizes.

3. Drug Facts Labeling

a. Purposes:

To the right of ibuprofen under Active ingredients, change ' ——— .. to "Pain reliever/fever reducer."

b. Uses:

(i) Remove ——— The indication is a more serious condition which may require medical attention, thus, is not appropriate for OTC use.

(ii) Add "common cold" after "temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies and."

(iii) Remove ' ——— from phrase "sinus ——— pressure."

(iv) Include "fever" as an additional bullet

c. Warnings:

Add "if you" to the subheading "Do not use."

Under that subheading, delete [redacted] from both clauses at the immediate right of the bullets.

Under "When using this product"

Add a 7th prebulleted statement "alcohol, sedatives, and tranquilizers may increase drowsiness."

Under "Stop use and ask a doctor if"

(i) Change [redacted] to "nasal congestion lasts for more than 7 days."

(ii) Change [redacted] to "fever lasts for more than 3 days."

(iii) Add as a 5th prebulleted statement "symptoms continue or get worse."

(iv) After "stomach pain occurs with use of this product," add "or if even mild symptoms persist."

d. Directions

For the direction "adults: take 1 caplet every 4-6 hours while symptoms occur," substitute [redacted] for "occur," and add a period followed by "If symptoms do not respond to 1 caplet, 2 caplets may be used."

e. Other information

Relocate "above" to precede 40°C.

B. Blister pack label:

Change company name from [redacted] to "Wyeth Consumer" before the term "Healthcare."

C. Pouch

a. Change Drug Facts labeling as in carton.

b. Change company name from [redacted] to "Wyeth Consumer Healthcare."

II. Inform the sponsor that the agency recommends the following:

A. inclusion of the established name "ibuprofen 200 mg, pseudoephedrine HCl 30 mg, chlorpheniramine maleate 2 mg coated tablets" on the Principal Display Panel of the carton and pouch dispenser labels.

B inclusion of subheading "Questions or comments?" a telephone number, and days and times of day of availability of someone to answer the telephone.

C. inclusion of "This package for household without young children." to be conspicuously labeled on the pouch dispenser.

III. HFD-550's Medical Officer should verify the accuracy of including the second dosage statement, "If symptoms do not respond to 1 caplet, 2 caplets may be used."

/S/

Michael T. Benson, R.Ph., J.D.
Regulatory Review Pharmacist

/S/

Concurrence, Marina Chang, R.Ph.
Leader, Team 1

/S/

Concurrence, Andrea Leonard-Segal, M.D.
Medical Officer

APPEARS THIS WAY

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/s/

Michael Benson
10/2/02 06:17:33 PM
INTERDISCIPLINARY

Marina Chang
10/3/02 08:12:20 AM
INTERDISCIPLINARY

Andrea Segal
10/4/02 08:48:00 AM
MEDICAL OFFICER

ANNOTATED LABELING

The proposed labeling for Advil® Allergy Sinus is based upon the following:

1. Approved labeling for Advil® Cold & Sinus Caplets (NDA 19-771 – approved September 19, 1989 for ibuprofen 200 mg/pseudoephedrine 30 mg). The labeling for Advil Cold & Sinus is based in part upon the approved labeling for Advil® Tablets (NDA 18-989 – approved May 18, 1984 for ibuprofen 200 mg). In addition, labeling is based upon the approval letter dated May 23, 2001 for NDA 19-771/S-020 (Advil® Flu & Body Ache Caplets - ibuprofen 200 mg/pseudoephedrine 30 mg).

2. Two Final Monographs contained in 21 CFR 341 "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use":

   A. Final Monograph for OTC Antihistamine Drug Products; Final Rule [57 FR 58356 (December 9, 1992)], and

   B. Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule [59 FR 43386 (August 23, 1994)].

   Particular reference is made to 21 CFR 341.12 and 341.72, and 21 CFR 341.20 and 341.80.

3. The "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use" Tentative Final Monograph for Combination Drug Products [21 CFR 341.40 and 341.85; 53 FR 30522 (August 12, 1988)].

4. Study AD-99-02, which was conducted to support the efficacy and safety of the product.

The final printed labeling will be formatted per the Drug Facts Rulemaking (21 CFR 201.66). The annotated labeling presented below indicates the support upon which the proposed labeling is based.

4 pages redacted from this section of the approval package consisted of draft labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: March 28, 2002

To: Mary Davis	**From:** Carmen DeBellas
Company: Wyeth Healthcare	Division of Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Fax number: 973-660-7187	**Fax number: 301-827-2531**
Phone number: 973-660-5825	**Phone number:** 301-827-2090
Subject: Information Request from Biopharm Reviewer for NDA 21-441 Advil Allergy Sinus Caplet	
Total no. of pages including cover: 1	

Comments:

Please ask to sponsor to address the following issue:

PK Comments:

In PK studies AD-99-01 and AD-99-03, the Tmax values reported by the sponsor for ibuprofen do not seem right. Looking at the ibuprofen profiles in both studies, Tmax appears to be around hours rather than around 1.7 hrs reported by the sponsor. Due to appearance of double peaks for ibuprofen in both studies, it is assumed that the computer picked Tmax value based on the first peak.

In light of that, the sponsor is suggested to look at data for the other components as that may also change some of the findings (e.g, food effect on pseudoephedrine, gender effect etc) they have reported in the submission.

Document to be mailed: ☐ **YES** ☑ **NO**

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/s/

Carmen DeBellas
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CSO

Carmen DeBellas
6/20/02 11:34:30 AM
CSO

TELECON MINUTES

TELECON DATE: November 29, 2001 **TIME:** 09:30 a.m. **LOCATION:** Corp S300

IND 61,725 **Telecon Request Submission Date:** September 17, 2001
Briefing Document Submission Date: 07-August-01

DRUG: Ibuprofen 200 mg/pseudoephedrine 30 mg/chlorpheniramine 2 mg

SPONSOR/APPLICANT: Whitehall-Robins Healthcare

TYPE of TELECON: PreNDA

FDA PARTICIPANTS:	**Office of Drug Evaluation V**
Jonca C. Bull, MD	Deputy Director, Acting Office Director
	Anti-Inflammatory, Analgesics, & Ophthalmic Drug Products
Lee S. Simon, MD	Division Director
Christina Fang, MD	Medical Reviewer
Stan Lin, Ph.D.	Statistical Team Leader
Jyoti Zalkikar, Ph.D.	Statistical Reviewer
Maria Rivera, Ph.D.	Pharm/Tox Reviewer
Sue Ching Lin, MS, R.Ph.	Chemistry Reviewer
Abi Adebowale, Ph.D.	BioPharm Reviewer
Barbara Gould	Project Manager
	Division of Over-the-Counter Drug Products
Charles Ganley, MD	Division Director
Daiva Shetty, MD	Medical Reviewer
Marina Chang, R.Ph.	Interdisciplinary Science Team Leader
Michael Benson, R.Ph., JD	Regulatory Review Pharmacist
Elaine Abraham, R.Ph.	Project Manager
Ansley Holland	Pharmacy Student
	Division of Pulmonary and Allergy Drug Products
Charles Lee, MD	Medical Reviewer

INDUSTRY PARTICIPANTS:	**Whitehall-Robins Healthcare**
Roger Berlin, MD	President, Global Scientific Affairs
Stephen Cooper, DMD, Ph.D.	Sr. Vice President, Global Clinical and Medical Affairs
Sharon Heddish, MD	Vice President, Regulatory Affairs Worldwide
Elizabeth Ashraf, Ph.D.	Sr. Director, Medical Communications
Hulon McCain, Ph.D.	Sr. Director, regulatory Affairs and Toxicology
Mary Davis	Director, Regulatory Affairs
Ken Warner	Director, Regulatory Affairs—CMC
Helen Fedoriw	Director, Regulatory Affairs—RQA/Submissions & Archives
Tailiang Xie, Ph.D.	Assistant Director, Biostatistics
Lawrence Marinucci, MS	Sr. Biostatistician
Lisa Tran, MSc	Sr. Manager, Regulatory Affairs
Erica Sinclair-Pabon	Associate, Regulatory Affairs—Submissions & Archives

BACKGROUND INFORMATION:

Advil Allergy Sinus is a pain reliever/nasal decongestant/antihistamine combination product. Its proposed indications are

INTRODUCTION:

It was agreed that we would dispense with the introduction of attendees and that an update list of the FDA attendees would be faxed to Whitehall following the teleconference. Prior to the teleconference draft responses to questions submitted in the briefing document were faxed to the company.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. ITEM 5: NON-CLINICAL PHARMACOLOGY / TOXICOLOGY

   (a) Does the Agency have any comments regarding the non-clinical pharmacology/toxicology section of this NDA?

   FDA Response:
   The evaluation of existing literature and the summaries of the two previously submitted teratology studies are sufficient to support this NDA. We do not have any further requests for pre-clinical studies at this time.

2. ITEM 6: HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

   (a) Dissolution and formulation history tables will be included in Item 4 CMC Investigational Formulations section, and will not be appended to the Item 6 Summary. Does the Agency find this acceptable?

   FDA Response:
   No, the sponsor should continue with their previous format of including the dissolution and formulation information in both Item 4 and Item 6 (the human pharmacokinetics and bioavailability section) in NDA submissions. This is also consistent with the recommendation in the guidance for industry entitled "Providing Regulatory Submissions in Electronic Format-NDAs".

   Whitehall made a counter proposal to have hyperlinks added from Item 6 (the human pharmacokinetics and bioavailability section) to connect directly to dissolution and formulation information in Item 4 (CMC section).

   The Agency found this to be acceptable.

3. ITEM 8D: CLINICAL DATA – CONTROLLED STUDIES / STATISTICAL ANALYSIS

(a) Are the revised statistical methods for the analysis of the efficacy and safety study (AD-99-02) acceptable to the Agency?

FDA Response:

Definition of ITT population:
The ITT population should be defined as "all randomized patients". All statistical analyses (including the one for SPID) should be performed for this population. The sponsor may provide additional analyses for the subsets of all randomized patients as described.

Prohibited medication
Subjects taking prohibited medications (concomitant analgesics, antihistamine, decongestant, or any combination of the three) should be treated as treatment failures.

Missing data procedures for reflective symptom scores:
The sponsor may provide sensitivity analyses by using Baseline Observation Carried Forward (BOCF) and Last Observation Carried Forward (LOCF) approaches to impute the missing reflective symptom scores.

Pain intensity scores:
SPID is the primary variable and since it is time-weighted sum of PID, it may be computed using the actual pain scores recorded by the subjects and the times at which they were recorded.

For example if pain intensity score is recorded at 2 hours and 3 hours after dosing, the SPID is computed as 2X+Y, where X is PID at 2 hours and Y is PID at 3 hours.

If pain intensity score is recorded at 100 minutes and 170 minutes then SPID may be calculated as (100/60)X+ (70/60)Y, where X is PID at 100 minutes and Y is PID at 170 minutes.

The approach proposed by the sponsor gives higher weights to the data near 3 hours and may potentially induce bias.

The missing pain scores could be imputed using LOCF and/or BOCF approaches before computation of SPID based on the two PID scores.

Additional comment:
The suggested morning or evening based LOCF is acceptable because of the time-related difference in allergy symptom response.

The sponsor's proposed interpolation method for the calculation of SPID is acceptable. However, the method of calculation proposed by our statistician should also be provided as part of the NDA submission.

Treatment by center interaction:
The proposed approach is acceptable.

Multiple Endpoints/Comparisons:
The step-wise approach proposed by the sponsor to control type I error rate is acceptable. At each step the treatment comparisons should be statistically significant at 5% level for EACH of the endpoints in order to proceed to the next step.

4. ITEM 8G: INTEGRATED SUMMARY OF EFFECTIVENESS (ISE)

(a) Does the Agency agree with the proposed assessment of demographic/drug, disease/drug, and drug/drug interactions?

FDA Response:

We have no objections to the proposed assessment of demographic/drug, disease/drug, and drug/drug interactions.

5. ITEM 8H INTEGRATED SUMMARY OF SAFETY (ISS)

(a) Whitehall-Robins plans to summarize the spontaneous adverse drug experience data by adhering to the format for the ICH PSUR, sections 6-9. Although there are no currently marketed products containing ibuprofen/pseudoephedrine/ chlorpheniramine, this safety review will include reports involving patients who concurrently took all three active drugs. Reports will be extracted from three sources:

- the sponsor's own spontaneous adverse event database for reports received up through September 15, 2001 (the "cut-off" date);
- non-Whitehall-Robins supplied reports contained in publicly available extracts of FDA's Spontaneous Reporting System (SRS) for the time period of January 1968 through October 1997;
- non-Whitehall-Robins supplied reports contained in publicly available extracts of FDA's Adverse Event Reporting System (AERS) for the time period November 1997 through first quarter 2001 (currently the latest update available).

Does the Agency find this approach acceptable?

FDA Response:

We have no objections to this approach; however, the safety data base for the concurrent use of the three active ingredient should also include worldwide safety reports as well as literature search.

(b) Similarly, Whitehall-Robins plans to summarize the overdose data involving patients who concurrently took all three active drugs. Reports will be extracted from two sources:

- the sponsor's own spontaneous adverse event database, and
- the American Association of Poison Control Centers (AAPCC) for the past five years.

Does the Agency agree with this proposal?

FDA Response:

We have no objections to this approach.

Additional Comment:

Cases of over dose from safety data base mentioned in 5a above should also be included in the summary.

(c) For the quarterly safety updates Whitehall-Robins plans to submit the following:

- for the marketed, single ingredient, ibuprofen-containing products, summaries of expedited reports received from spontaneous sources starting with September 16, 2001, i.e. after the "cut-off" date of September 15, 2001;
- for the marketed, combination product containing ibuprofen and pseudoephedrine, summaries of expedited reports received from spontaneous sources starting with September 16, 2001;
- any new overdose reports received since September 16, 2001 in the sponsor's own spontaneous adverse event database describing patients who concurrently took all three active drugs;
- when available from AAPCC, an update of the overdose data involving patients who concurrently took all three active drugs;
- any new literature reports involving patients who concurrently took all three active drugs.

Does the Agency have any comments regarding the safety updates?

FDA Response:

We have no objections to this approach.

The sponsor asked if it was necessary to submit the quarterly safety update since there is not another triple combination product with the same ingredient currently marketed.

The Agency agreed that the quarterly safety reports are not required provided that no new studies with the same ingredients are initiated.

6. ITEM 20: OTHER – REQUEST FOR WAIVER OF PEDIATRIC STUDY REQUIREMENTS

   (a) Does the Agency agree to waive the pediatric study requirements for this product?

   FDA Response:

[ ]

7. ELECTRONIC SUBMISSION

   (b) Does the Agency have comments on this section?

   FDA Response:

   Please provide 2 additional clinical reviewer copies.

Action Items:

1. Minutes of the teleconference will be conveyed to the sponsor within 30 days.

/S/

Barbara Gould Date
Project Manager

/S/

Jonca C. Bull, MD Date
Deputy Director, ODEV
Acting Office Director, ODEV

Initialed by: JZalkikar/*30-Nov-01*
MRivera/*30-Nov-01*
CLee/*30-Nov-01*
AAdebowale/*04-Dec-01*
EAbraham for OTC/*05-Dec-01*
CFang/*05-Dec-01*
LSimon/*05-Dec-01*

TELECON MINUTES
Minutes faxed and DFS'ed:

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

/s/

Jonca Bull
12/6/01 04:07:13 PM