CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-076

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-076 SUPPL # _

Trade Name Aleve Cold and Sinus Generic Name naproxen sodium and pseudoephedrine hydrochloride

Applicant Name Bayer Corporation Consumer Care Division HFD- 550

Approval Date, if known Nov. 29, 1999

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 question about the submission.

   a) Is it an original NDA?

   YES /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /___/

   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 /___/ 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.

   _____

   _____

   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:

   _____

   _____

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?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 8.

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

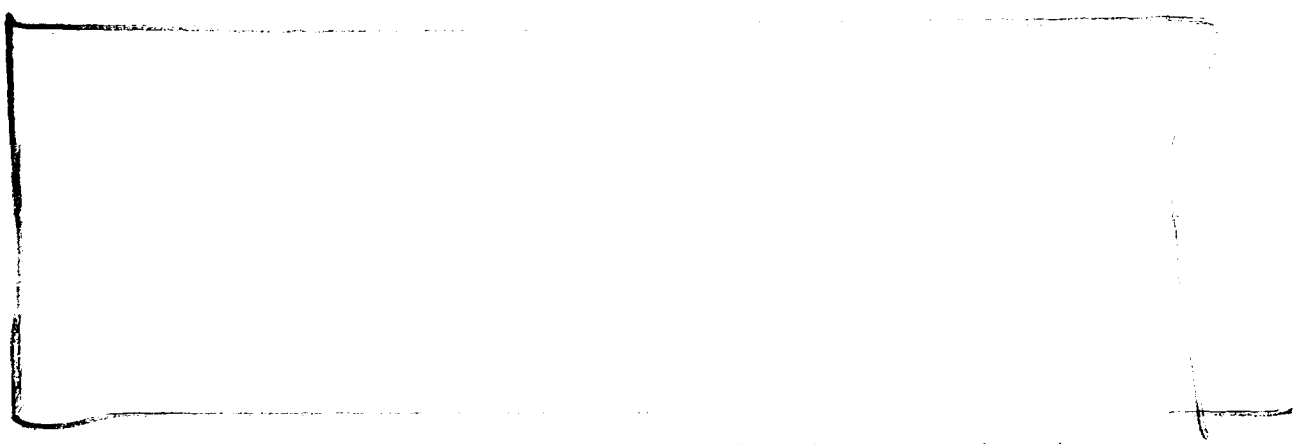
YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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.



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 /X/ NO /___/

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

NDA# 17-603 pseudoephedrine HCl

NDA# 20-204 naproxen sodium

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. 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 8.

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.

(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 8:

_____

_____

YES /___/ NO /___/

(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 /X/ NO /___/

(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 /X/

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 /___/

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:

S 97-051

S 97-052

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 S97-051 YES /___/ NO /_X_/

Investigation #2 S97-052 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:

_____ _____

_____ _____

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_/

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

_____ _____

_____ _____

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"):

S97-051 _____

S97-052 _____

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 # [redacted] YES /_X_/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # [redacted] YES /_X_/	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: _____

_____

_____ _____

Signature Date

Title:_____

/S/ M.D. Nov 29 1999

Signature of Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APR 3 2000

LABELING REVIEW OF NDA

NDA #21-076 (FA)

Submission Date: 3/15/2000
Review Date: 04/03/2000
Reviewer: Cazemiro R. Martin

Applicant:
Bayer Corporation
Consumer Care Division
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910

Applicant's Representative:
Craig Hammes
Director,
Regulatory Affairs

Drug:
ALEVE COLD & SINUS
naproxen sodium and pseudoephedrine hydrochloride
extended-release tablet, 220 mg/120 mg

Pharmacologic Category:
Paine reliever/Fever reducer/Nasal decongestant

Submitted:

- Consumer labeling leaflet
- 10-caplets count carton
- 20-caplets count carton

Reviewer's Comments:
The final printed labels and labeling are identical to the draft as requested in our approval letter dated November 29, 1999. However, the sponsor did not submit a final printed label and labeling as requested in our approval letter for its Aleve Cold & Sinus blister pack packaging.

Recommendation:
The labeling for the submitted package sizes is acceptable and an "Acknowledge and retain" letter should be issued to the company. In addition, the sponsor should be informed that it should submit the final printed labeling (FPL) of its blister pack backing when available.

IDS: Cazemiro R. Martin

NOV 2 1999

Addendum NDA Labeling Review

NDA # 21-076

Submission Date : 1/28/99
Amendment Date : 8/12/99
Review Date : 10/13/99

Applicant: Bayer Corporation
Consumer Care Division

Applicant's Representative: Rich Cuprys
Associate Director
Regulatory Affairs

Drug: ALEVE COLD & SINUS
naproxen sodium and pseudoephedrine hydrochloride
extended-release tablet, 220 mg/120 mg.

Pharmacologic Category: Pain reliever/Fever reducer/Nasal decongestant

Submitted: General Correspondence - Proposed Pouches for Non-Saleable Distribution

- Attachment 1: Direct Mail Pouch
- Attachment 2: Preferred Format for Professional Sampling
- Attachment 3: Direct Mail Pouch and Alternate Format for Professional Sampling

Reviewer Comments:

A. Attachment 1: Direct Mail Pouch

1. The outer card must have Drug Facts labeling as described in 21 CFR 201.66 and any other labeling that may be required. The pouch must be attached (or glued) to the card to prevent the separation from the card.

2. The phrase "Not for Resale" should prominently and conspicuously appear on the front of the card and on the front of each 1-count pouch.

3. The phrase "See Drug Facts information on the back panel" or other similar statement should appear on the front or inside of the card which specifically directs the consumer to the area (i.e., back panel) of the outer card where the Drug Facts information appears.

4. The information on the 1-count pouch is not readable, and therefore should be revised to provide labeling that is readable. Further, because the attached card with full Drug Facts labeling

is considered the outer container, the labeling required for the inner package (1-count pouch) is described in 21 CFR 201.10(i) and in 21 CFR 201.60 through 201.62, and must include any other applicable information required by regulation or OTC drug monograph.

B. Attachment 2: Preferred Format for Professional Sampling

1. "Not for Resale" must appear on the front of each 1-count pouch and on the dispenser box.

2. The 1-count pouch is to be supplied to a medical degree professional (as agreed to by the Sponsor) for distribution. They should not be distributed to retail outlets or their employees.

3. The full Drug Facts labeling should appear on the dispenser box. Individual pouches without a dispenser box should not be provided to the medical degree professional. The medical degree professional or their designee can provide the pouches to patients.

4. The information on the 1-count pouch is not readable, and therefore should be revised to provide labeling that is readable. As indicated in the Sponsor's letter, the pouches would be distributed in a dispenser box with full Drug Facts labeling. Therefore, the full Drug Facts labeling for the 1-count pouch is not required. However, the 1-count pouch must include labeling described in 21 CFR 201.10(i) and in 21 CFR 201.60 through 201.62, and must include any other applicable information required by regulation or OTC drug monograph. Based on these labeling requirements, the type style and size should be revised to provide more readable labeling.

5. Although optional, the agency recommends that the Sponsor provide the medical degree professional with a supply of hand-out copies of the full Drug Facts labeling to be distributed at the same time the 1-count pouch is provided to the consumer.

C. Attachment 3: Alternate Format for Professional Sampling

1. The package insert that contains Drug Facts information is not clearly marked. Because full Drug Facts labeling as described in 21 CFR 201.66 cannot appear on the 1-count pouch, a statement should appear on the PDP panel of the 1-count pouch directing the consumer to read the attached package insert containing the Drug Facts information.

2. If the Sponsor wants to use this package configuration as an alternate for the preferred professional sampling with a dispenser box, the agency will not object providing that the full Drug Facts labeling appears on the dispenser box.

3. The same comments and revisions as indicated for Attachment 2 (see B1, 2, and 4) apply to this Attachment.

Recommendations:

1. The agency is reserving final approval of the proposed pouches for non-saleable distribution until the Sponsor has revised each of the proposed pouches as recommended by the agency and has submitted mock-up labeling for (a) The card in Attachment 1, (2) each non-saleable pouch, and (3) the dispenser boxes intended for professional sampling as described in Attachments 2 and 3 of the Sponsor's submission.

2. With reference to Attachment 1 of the Sponsor's submission (i.e., outer envelope with 1-count non-saleable pouch inside), the agency recognizes that although the outer envelope is required to include the full Drug Facts labeling, the immediate container is not required to meet the format requirements of 21 CFR 201.66. However, the Sponsor should be informed that the immediate container must contain any information that is described in 21 CFR 201.10(i) and in 21 CFR 201.60 through 201.62, and must include any other applicable information required by regulation or OTC drug monograph.

3. With reference to Attachment 2 of the Sponsor's submission (i.e., Preferred Format for Professional Sampling), although optional and contingent upon the agency's approval of this 1-count pouch drug sample for professional sampling, the agency recommends that the Sponsor provide the medical practitioner with a supply of hand-out copies of the full Drug Facts labeling to be distributed at the same time the 1-count pouch is provided to the consumer.

4. Inform the Sponsor that the proposed pouches for non-saleable distribution must be distributed only to a medical degree professional and are not to be given to any retail establishment or its employees for distribution.

/S/

IDS: Cazemiro R. Martin
11/1/99

OTC /DDMAC JOINT REVIEW

AUG 30 1999

NDA#: 21-076
Drug: Aleve Cold and Sinus
(naproxen sodium 220 mg/pseudoephedrine HCL 120mg)
Sponsor: Bayer Corporation Consumer Care Division
Study: Label Comprehension Study, number S98-064
Submitted: January 28, 1999
Received: February 1999
Reviewed: July 16, 1999

The label comprehension study for Aleve Cold and Sinus submitted for review, had as its primary objective to test the effectiveness of the package label in communicating indications, directions for use, and warnings. This study was performed from November 25, 1998 to December 11, 1998 in sixteen geographically dispersed areas across the US. The study population consisted of 390 participants divided into three subgroups: a random sample of 286 subjects, an augmented low literacy group of 57 subjects with a REALM literacy test reading level below ninth grade, and an additional supplement of 47 subjects who had used Aleve within the past year. The total proportion of low literacy subjects was 90/390 (23%) which included 33 subjects from the random sample, and the total proportion of previous Aleve users was 116/390 (30%). The age and gender distributions were as follows: 18-34 (33%), 35-49 (33%), and >50 (33%), males (40%) and females (60%). All participants were 18 years of age or older.

The study was performed at sixteen sites, identified in the protocol as shopping malls. At each site, three or four professional interviewers were used, each being responsible for up to eight interviews. The questionnaire contained the verbatim language to be used by the interviewers when speaking with the subjects. Each interviewer contacted and screened a designated number of adults at various locations in the sites at different times of day, including working and non-working women. Each consumer was given a prototype package label exhibit to read as if they were deciding whether or not to purchase the product. The tested label exhibit was in a "finished appearance", at the actual size. It was not, however, in the currently required Drug Facts format, and revisions have subsequently been made in the contents as listed in Table 1.

Table 1

Sponsor's Proposed Revisions to Label

- The references to sinus pain and sore throat have been removed from the **Uses** section.
- The last bullet in the **Stop use and ask a doctor if** section referring to sore throat has been removed.
- The **Directions** section now includes the statements, "Do not crush or chew. Swallow whole."
- The storage condition now reads, "Store at 20 to 25°C (68-77F)".

These label revisions were made following a meeting on Dec 16, 1998 with representatives of the FDA. Bayer believes that these changes do not significantly affect the results or conclusions of the label study. The OTC division is also preparing a separate labeling review.

Study Results

The written self-administered questionnaire consisted of label-based questions (to be answered with the label in view). Open-ended and closed-ended questions were used. For the open-ended questions, consumers were required to provide answers in their own words without prompting. For the closed-ended questions, three to five possible answers, one or more of which were correct, were listed explicitly for each question, and consumers were asked to select the correct answer(s) from the list. Two additional questions were asked orally by the interviewer and were recall-based (to be answered without the label in view).

The questionnaire format may have produced a response bias, because questions 18-24 in sequence were all, except for question 22 (Q22), asked in a form such that the correct answer was "no". Question 22 (dealing with the MAOI warning and drugs for depression, psychiatric or emotional conditions and Parkinson's) had a notably lower correct response rate than the others in the sequence.

Symptoms Treated (Q2,5,7,9)

These questions tested the understanding of the symptoms treated by the product. Results are summarized in the table below. For Q2, the subjects were asked to list indications without the package label in view. For Q5, the subjects were asked to list the indications with the package label in view. The correct response rates were higher for Q5, as would be expected (see Table 2). The use of open-ended questions to elicit a list of items usually results in incomplete data. Typically, participants mention only some of the items in the list, but not all. Nine percent (9%) of the low literate could not give a response to this question.

Table 2 **Indications recalled by >10% of consumers**

	Q2 without label in view	**Q5 with label in view**
headache	49%	65%
nasal congestion	37%	69%
sinus congestion	32%	62%
fever	29%	45%
pain	30%	44%
body aches	30%	60%
sore throat	26%	57%
cold	26%	22%
sinus	21%	17%
sinus pain	18%	52%
sinus pressure	15%	51%
flu	13%	21%

Questions 7 and 9 presented lists of symptoms for participants to identify as being treated or not treated by the product. In general, consumers picked the correct answers at least 80% of the time. For Q7, 66% got all 4 choices correctly; for Q9, 81% got all 3 correct. However, there is no indication as to how many who got these correct also made the incorrect choice in each question. For both questions, about 15% chose the incorrect symptoms—arthritis and nausea. Aleve users were more likely to choose the former incorrect answer (about 25%), possibly because Aleve is known as an analgesic medication and is indicated for "relief of aches and pains associated with minor arthritis."

The responses to these 4 questions suggest that there is an understanding that a variety of symptoms are treated by the product; however, it is not clear whether consumers understand that the product treats a combination of symptoms related to cold and flu.

Ask the Doctor Before Use (Q3, 4, 10, 11, 13, 19, 22, 24)

These questions dealt with situations in which the consumer should consult a physician before using the product. The low literate participants appeared to have problems with warnings about the use of other drugs. Q22 confuses the warnings regarding asking a doctor before use with those presenting contraindications that stated who should not use the product at all. However, this distinction may not be important for consumers if they are inclined to ask a doctor in either case.

Question 3 asks participants to recall who should ask a doctor before use. This question is asked without the product label in view. One condition (heart disease) scored at 50%. The rest were lower. Question 4 is similar; however participants can refer to the label before responding (see Table 3). For this question, 69% provided the heart disease response, with the rest at a lower level. In response to this open-ended question, few (20% or less) gave responses relating to drug interactions, serious side effects from any pain reliever, being under a doctor's care for a chronic condition, pregnancy, breast feeding, use of MAOI's, drugs for Parkinson's disease, or having 3 or more alcoholic drinks a day. Again, the use of open-ended questions to elicit a list of items usually results in incomplete data.

Table 3 Conditions for which a doctor should be consulted before product use

	Q3 without label in view	Q4 with label in view
heart disease/heart conditions	50%	69%
high blood pressure	47%	67%
diabetes	25%	57%
thyroid disease	26%	53%
pregnancy	26%	8%
do not use if you are taking other drugs on a regular basis	14%	20%
difficulty urinating due to enlargement of prostate gland	13%	47%
do not use if taking MAOI	7% (1% low lit)	5%
doctor's care for any continuing condition	3%	12%
Parkinson's disease	5%	4%
breast feeding	4%	3%
3 or more alcoholic drinks a day	3%	2%
serious side effects from any pain reliever	2%	10%

The remainder of the questions on the topic of who should consult a doctor before use involved either multiple-choice questions (in which more than one choice may have been correct) or yes/no questions. The rate of correct responses generally exceeded 80% in these questions. In Q11, 74% of the low literate subgroup answered correctly that people who have serious side effects from any pain reliever should not use Aleve Cold & Sinus before asking a doctor first.

The question about drinking alcohol (Q13) showed that 19% did not understand this warning. For Q19, 28% of the low literate subgroup incorrectly responded that it is appropriate to take Aleve Cold and Sinus without consulting a doctor if one is taking other drugs on a regular basis. These warnings were not communicated adequately by the study label.

The question about whether a doctor should be consulted before use if one takes drugs for depression, psychiatric or emotional conditions or has Parkinson's Disease (Q22) showed that a large proportion did not understand the warning (29% of the random group was incorrect; 3% did not know) and that even more low literate had problems responding (42% incorrect; 8% did not know). These results may be attributable, in part, to a misinterpretation of the question. For example, some participants may have believed that

a "no" response meant they should not take the product, when it really meant they should not see a doctor. Further, they may have read the label carefully enough to notice that it did not recommend consulting a doctor in these situations—only not taking the drug. Alternatively, this low correct response rate (69%; 50% low literate) may be due to the placement of this information about drug interactions in a paragraph. In addition, this question may have been affected by response bias, since it was the only question in a sequence of seven where the correct answer was "yes".

Contraindications (Q18, 20,21,22)

Several questions related to contraindications on the label that stated who should not take the drug at all. Comprehension was fairly good for the allergy question (Q18; 93%) and the questions about use of other pain relievers (Q21; 87%) and MAOI drugs (Q20; 91%). However 8% of the low literate subgroup responded that they could take Aleve Cold & Sinus if they ever had an allergic reaction such as hives or asthma after taking a pain reliever or fever reducer, which could have serious consequences. Participants did not correctly answer the question about use with psychiatric drugs or drugs for Parkinson's disease at a high rate (Q22; 69%; 50% low literate; see the above discussion).

Dosing (Q6, 14-17)

The open-ended question about dosing (with the label available) produced a 93% correct response rate for the random sample; 87% for the low literate. Seven participants stated that the correct dose of Aleve Cold & Sinus was once every 4 hours. Ten percent (10%) of the low literate could not or did not respond. One closed-ended dosing question (Q14) showed that 88% of the random sample were correct; however 77% of the low literate were correct and 17% of that group incorrectly responded that 2 tablets every 12 hours would be appropriate.

When asked how many days one could take Aleve for colds (Q16), 83% of the random sample and 73% of the low literate correctly responded with 7 days; 21% of the low literate responded 4 days. A similar question about fever produced the same percentages of correct responses (3 days); however 12% of the low literate said 1 day, 10% said 5 days, and 3% said 9 days.

Thus the low literacy subjects had difficulty comprehending the dosing directions. Seventeen percent of the low literate population responded that twice the recommended dose was the correct adult dose, and 7 participants responded that three times the recommended dose was correct.

When to Stop Use (Q8,12)

When asked a closed-ended question listing possible conditions for which one should stop using the product, only 50% got all 4 choices correct (37% of the low literate). The fewest correct responses were given for "develop heartburn," which was chosen by 63% of the random population and 56% of the low literate. "Develop symptoms of nervousness, dizziness or sleeplessness" was chosen by 82% of the random population and 71% of the low literate. Question 12 provided 4 more correct choices and one incorrect. Fifty-three percent of the random group and 38% of the low literate group correctly answered all 4. The response of "stomach pain" was the correct response least likely to be chosen (73% random; 58% low literate). Participants chose "difficulty swallowing" at a similar rate (77% random; 58% low literate). These results suggest that these warnings about when to stop use may not be clear.

As these warnings are already in bullet form, a format change will not help the comprehension of this information. These warnings are in a fairly long list, which consumers may have trouble reading.

Use in Children
Participants correctly answered the question about use in children at a high rate (92%).

Conclusions

Consumers had problems understanding material that appeared in paragraph form. This included warnings about alcohol and drug interactions. The low literate group had problems with dosing directions. These problems should diminish when the label is placed in the Drug Facts format. However, some participants also had difficulty understanding the conditions under which consumers should stop use and consult a physician. This information was already in bullet form on the tested label.

The label would benefit if the following changes were made:

- It presents the indications in a way that indicates that there is a cluster of related symptoms to be treated.
- More information is put in bullet form, rather than paragraph form.
- Dosing directions are bolded or emphasized in some other way.
- Situations in which the drug should be stopped and a doctor consulted is combined into a shorter list.
- MAOI warning is clarified to a simple "Do not use."
- Bold the allergy warning.
- Warnings about heartburn and dizziness should be conveyed more clearly.

In conclusion, the comprehension results from this label study reveal areas of the labeling that could be improved. Many of the difficulties should be ameliorated by conversion of some of the information to bulleted form and bolding in other cases. Since this is essentially a combination of monograph and NDA labeling, and since there is a fair amount of overlap in the warnings, the above changes along with the redundancy in the warnings should ameliorate many of these difficulties.

/S/

Linda Hu, M.D.
Medical Officer, DODP
HFD-560

/S/

Karen Lechter, J.D., Ph.D.
Social Science Analyst
HFD-40

/S/

Linda M. Katz, M.D., M.P.H. 9/16/99
Deputy Director, DODP
HFD-560

Meeting Minutes- 4/28/99

IND [redacted]
NDA 21-076
DRUG Aleve Cold and Sinus
(naproxen sodium 220 mg and pseudoephedrine HCl 120 mg)

PURPOSE Discussion of CMC Issues

PARTICIPANTS

FDA: Dennis Bashaw, Pharmacokinetics; Sue-Ching Lin, Chemistry; Assadollah Noory, Pharmacokinetics; Hasmukh Patel, Chemistry Team Leader

BAYER: Anthony Ekpe, Analytical Development; Craig Hammes, Regulatory Affairs; Richard Ho, Product Development; Karen Mancuso; Regulatory Affairs; George McCauley, Regulatory Affairs; Annette Owens, Analytical Development; Bill Walsh, Regulatory Affairs; Maw-Sheng Wu, Analytical Development

FDA prepared the meeting discussion points, which were faxed to Bayer. Bayer prepared a written reply to the discussion points, which was provided to the FDA prior to the teleconference. During the meeting the discussion points were reviewed in detail.

FDA Discussion Point #1:

Specifications and Analytical Methods for the Finished Dosage Form: Volume 5, pages 40-43:
Two dissolution methods are listed. Please identify only one method that is to be used for the regulatory specifications.
Dissolution time points and ranges will also be discussed.

Bayer Written Response:

[redacted]

We look forward to the discussion on the dissolution time points and ranges.

Teleconference Discussion

- FDA requested that Bayer perform a [redacted] analysis on the clinical data for study #S97-050, the four way crossover bioavailability study, to attempt to explain the T_{max} results from the PK studies. FDA agreed that the duration of the product efficacy was not being questioned.
- Bayer will follow up directly with Dennis Bashaw with respect to this issue.

- FDA requested that the [redacted] specifications at the [redacted] hour time point be re-evaluated for pseudoephedrine HCl. Bayer agreed to reevaluate the current specifications and will provide FDA with proposed revised specifications.

FDA Discussion Point #2:

Manufacturing processes for pseudoephedrine HCl [redacted]
Please state whether the processes used in manufacturing the investigational formulations and the production batches are identical. It was noted that the [redacted] for investigational formulations were obtained from [redacted] However, pseudoephedrine HCl [redacted] will be manufactured at [redacted]

Bayer Written Response:

The processes used in manufacturing the investigational formulation and the production batches are identical. The equipment involved in the manufacturing of the investigational formulations and the production batches varied only in working capacity. The formula and process for the pseudoephedrine HCl [redacted] was successfully transferred from [redacted] which was the site of the registration batch manufacturing.

Teleconference Discussion

- Bayer reiterated that the processes used to produce the clinical batch and those used to produce the registration batches were identical.
- Bayer stated that a confirmatory study was conducted to link the pharmacokinetics of both batches (Study S98-068).
- FDA requested a summary of the chemical data comparing the clinical and registration batches. Bayer agreed to provide this information.
- Bayer confirmed that there will be no reprocessing of this product.

FDA Discussion Point #3:

Please provide quantitative compositions of [redacted] Please provide 21 CFR citations, if applicable, for the ingredients contained in the above two formulations.

Bayer Written Response:

Attached to this memo please find the information you requested.

Teleconference Discussion

- FDA was satisfied with this information.

FDA Discussion Point #4:

Container/Closures: Please provide a detailed description of the container/closure systems. Information such as number of blisters in a blister card, number of blister cards or pouches contained in a carton, and the packaging process should be provided.

Bayer Written Response:

The following is the intended distribution of the product:

a. **10- count carton-** will contain 1 blister card, with 10 tablets per blister card, 1 tablet per blister
b. **20- count carton-** will contain 2 blister cards, with 10 tablets per blister card, 1 tablet per blister
c. **1- count Pouches-** will be used as individual samples

The blister presentations will be produced [redacted] The pouches will be produced [redacted]

Teleconference Discussion

- FDA was satisfied with the description of the intended product distribution
- FDA requested a stepwise description of the packaging processes. Bayer agreed to provide this information.

FDA Discussion Point #5:

Packaging Equivalency Protocol [volume 5, page 29] is not acceptable. Test results should be submitted as a prior approved supplement before a change in container/closure system is made.

Bayer Written Response:

We would like to address this issue further in the meeting. We are interested in discussing ways to amend this protocol to bring it in line with your expectations.

Teleconference Discussion

- Bayer assured the Agency that this protocol is intended for applications related to this product only.
- FDA agreed to look into this further and will get back to Bayer.

FDA Discussion Point #6:

Stability Protocols [volume 5, page 79]: in addition to the time points specified on page 79 the following intervals are required:

Bayer Written Response:

We will comply with these requests.

Teleconference Discussion

- Bayer will provide the revised protocol to the FDA in Word 97 electronic format.

FDA Discussion Point #7:

Stability data on pilot batches and clinical batches may be submitted as supportive information.

Bayer Written Response:

We currently have the following data available:
12-month data on a pilot batch (initiated October 1997)
12-month data on the clinical batch (initiated November 1997)

We are interested in discussing this topic at the meeting.

Teleconference Discussion

- Bayer confirmed these batches were manufactured using the same operating principles as the registration batches. Different blister materials were used for the stability studies.
- Bayer agreed to provide a summary of the data from these batches

FDA Discussion Point #8:

Regulatory and stability specifications:
Please list the analytical methods that are used for each parameter. If methods are compendial methods please indicate so. We prefer that you tabulate specifications in the format of tests, methods, and acceptable limits (specification).

Bayer Written Response:

We will revise our table to include the methods numbers as you requested. A copy of these specifications in the revised format will be forwarded to you when they become available.

Teleconference Discussion

- Bayer will provide a revised copy of these specifications in the requested format
- Bayer will provide an electronic copy of these specifications electronically in Word 97.

NOTE- Following the teleconference, FDA requested (via e-mail) specifications for moisture content for the drug product, for both release and stability. Bayer will communicate with the review chemist to clarify this request.

FDA Discussion Point #9:

Pseudoephedrine hydrochloride has a known degradation profile. Please set specifications for degradation products of pseudoephedrine hydrochloride.

Bayer Written Response:

Although the degradation profile for pseudoephedrine is known, so far our stability results indicate the compound is stable in our formula. Pseudoephedrine products in USP also do not include degradation products in its specifications. Our supplier [redacted] indicated that no degradation was found in the drug substance up to [redacted]

We look forward to discussing this with you in the meeting.

Teleconference Discussion

- Bayer agreed to continue to search for adequate methods to address this request.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

NDA 21-076
DRUG: Aleve Cold & Sinus
COMPANY: Bayer
DATE: April 8, 1999

RE: FDA new Ruling for OTC labeling/Drug facts

PARTICIPANTS:
FDA -Cazemiro Martin, OTC reviewer and Sharon Schmidt, Project Manager

Bayer- Karen Mancuso and Rich Cuprys, Reg. Affairs

Bayer was explaining that they were having difficulty getting all of their drug facts on a 2X 3 in pouch using a 4.5 font size printing. The pouch would either need to be bigger or the font would need to be 6.0 in order to get all the info required onto the pouch. The problem was also amplified by the fact that not many or Bayer's pouches (5 out of 20) are sold with an outer container/carton. They suggested that other companies will be having the same problem.

The sponsor was told that the FDA was aware of this issue and it is scheduled to be discussed at the April 23 feedback committee meeting. In the mean time they should try to use the new ruling language to save space on the pouch. They will have to implement the new labeling at the time they first market the new drug product. Dr. Martin requested that they provide an actual pouch to him as soon as available.

Second Telcon Mr. Martin called to remind them that the outer tray theoretically contains several unit dosage packets and may not be the outer container on which to include the Drug Facts information. I pointed out that in most instances the consumer is going to take the product home and use it at a later time. Required information that addresses "While using this product" or "Stop use if....." or "Directions" must be available at the time the consumer purchases the product. We would certainly like such information to also be available at time of actual use meaning on each dose/unit packet but this is not a requirement. I added that if such packets are in a tray, this outer tray may not be the appropriate place for such information and that the unit packet may still be required to contain the required information for the safe and effective use of the product. This would especially be true if the packets are meant to be bought one at a time. It has not been determined that the outer tray is the outer container on which to include the Drug Facts information. Decision is pending.

Karen Mancuso appreciated my call back and understood the possibility that a tray presentation

containing individual drug packets may not be an acceptable place to satisfy the new OTC labeling requirements. The conversation ended amicably with intentions to work together to resolve NDA labeling issues.

cc: NDA 21-076
Div. File
HFD-550/S.Schmidt
HFD-560/C.Martin

JAN 28 2000

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 28, 2000

FROM: Leslie Vaccari /s/ 1-28-00
Acting Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

TO: Rosemary Cook
Chief, Project Management Staff
Division of Over-the Counter (OTC) Drug Products, HFD-560

SUBJECT: Transfer of NDA

Pursuant to the Center policy of placing administrative responsibility of INDs with the Division which reviews the proposed clinical usage of the drug, I am forwarding the attached for your acceptance.

NDA 21-076 Aleve Cold and Sinus (naproxen sodium and pseudoephedrine hydrochloride extended-release tablet) 220 mg/120mg was approved November 29, 1999. This new drug application provides for the over-the-counter use of Aleve Cold and Sinus for the temporary relief of cold, sinus and flu symptoms.

If you concur, please notify HFD-92, Central Document Room and HFD-550 by copy of this memo.

CONCUR /S/ 1/28/2000 NON-CONCUR _____
REASON:

cc: ORIG. NDA 21-076
DIV. FILE
HFD-92
CDR
HFD-550 Doc. Room
HFD-550/SSchmidt
HFD-550/LVaccari/1-28-00