CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-076

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY - 4 2000

NDA 21-076

Bayer Corporation
Attention: Mr. Craig Hammes
Director, Regulatory Affairs
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910

Dear Mr. Hammes:

We acknowledge the receipt of your March 15, 2000 submission containing final printed labeling in response to our November 29, 1999 letter approving your new drug application (NDA) for ALEVE COLD & SINUS (naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg).

We have reviewed the labeling that you submitted in accordance with our November 29, 1999 letter, and we find it acceptable. However, we also need you to submit the final printed labeling of the blister pack backing when it becomes available.

If you have any questions, call Babette Merritt, Project Manager, at (301) 827-2222.

Sincerely,

/S/

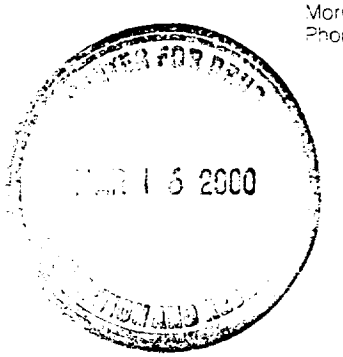
Maria Rossana R. Cook, M.B.A.
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone 973 254-5000

March 15, 2000



NDA No. 21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

Charles Ganley, MD
Director
Division of OTC Drug Products (HFD-560)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Building 2, 2nd Floor
Document Control Room N-115
Rockville, Maryland 20850

Subject: Final Printed Labeling for Approved NDA 21-076

Dear Dr. Ganley:

Please refer to our New Drug Application (#21-076) for Aleve® Cold & Sinus and to Agency approval letter dated November 29, 1999.

Appended please find 20 copies of the following final printed labeling as requested in the NDA approval letter:

- consumer labeling leaflet
- 10-count carton
- 20-count carton

If there are any questions regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

/S/

Craig Hammes
Director,
Regulatory Affairs

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA 21-076
Aleve ® Cold and Sinus Caplets
(naproxen sodium 220 mg and
pseudoephedrine HCl 120 mg SR)-OTC

March 3, 2000

Charles Ganley, MD, Director
Division of OTC Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn.: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Subject: **Special Supplement- Changes Being Effected in 30 Days**
Revision of Pseudoephedrine HCl Supplier DMF

Dear Dr. Ganley:

In accordance with 21 CFR § 314.70, Bayer Corporation hereby submits a supplemental application to NDA 21-076 providing notice that our supplier of [redacted] pseudoephedrine hydrochloride has submitted to the Agency a fully revised update of their drug master file. Our pseudoephedrine hydrochloride supplier, [redacted] has updated their [redacted] pseudoephedrine hydrochloride drug master file [redacted] to reflect a change in the synthesis process of the key intermediate, [redacted] ephedrine hydrochloride. We understand that the [redacted] pseudoephedrine hydrochloride synthesis process has not been changed. [redacted] is referenced in our NDA 21-076.

[redacted] ephedrine hydrochloride for commercial sale, as well as for use in the synthesis of pseudoephedrine hydrochloride and pseudoephedrine sulfate. [redacted] has updated their DMF for ephedrine hydrochloride [redacted] to incorporate the synthesis process change.

Bayer was informed by [redacted] epresentatives that FDA lead reviews of the updated master files for [redacted] pseudoephedrine hydrochloride [redacted] and [redacted] ephedrine hydrochloride have been completed. As directed by the Agency, [redacted] has informed us that we are obligated to submit a "Changes Being Effected in 30 Days" supplement to NDA 21-076 notifying the Agency of the update to [redacted]

ORIGINAL

To fulfill our regulatory obligations as delineated by the Agency in its discussions with [redacted] Bayer commits to placing the first production batch of Aleve Cold & Sinus made with pseudoephedrine hydrochloride produced from the new process ephedrine hydrochloride in our commercial product stability program. Stability data on this batch will be submitted to the Agency in the product annual reports. Bayer will notify the Agency if an uncharacteristic change in the product is observed during stability evaluation.

Should you have any questions or require additional information, please contact Bill Walsh at 973-408-8046.

Sincerely,

Craig Hammes
Director, Regulatory Affairs
Bayer Corporation
Consumer Care Divison

submitted in duplicate

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

February 25, 2000

NC

NDA No. 21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

Charles Ganley, MD
Director
Division of OTC Drug Products (HFD-560)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Building 2, 2nd Floor
Document Control Room N-115
Rockville, Maryland 20850

Subject: Amendment to Pending Supplement
Proposed Pouch/Consumer Card/Professional Dispenser Box

Dear Dr. Ganley:

Please refer to our New Drug Application (#21-076) for Aleve® Cold & Sinus (approved November 29, 1999) and to our Labeling Supplement dated January 5, 2000. Reference is also made to Thomas Parmelee's request for information regarding the font size utilized on the pouch, consumer card, and professional dispenser box. Please note that drug facts labeling for the consumer card and dispenser box are exactly as approved in the Original NDA. Following please find the requested font information:

Pouch

6pt Type, 6.25pt Leading

Consumer Card & Dispenser Box

Title 14 pt Bold Italic
Headings 8 pt Bold Italic
Sub Headings 6 pt Bold
Text 6 pt
Leading 6.5 pt
Bulleted Statements 6 pt
Thick Rules 2.5 pt
Thin Rules .5 pt

ORIGINAL

Tom Parmelee also requested that Bayer provide information describing how we intend to adhere the pouch to the consumer cards. Bayer intends to spot glue each pouch to the consumer cards.

If there are any questions regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Craig Hammes
Director,
Regulatory Affairs

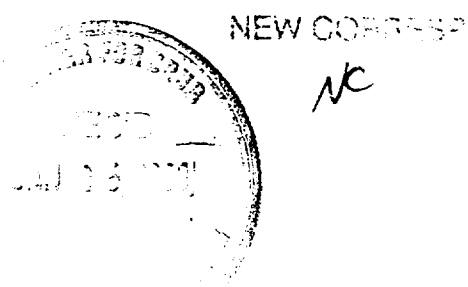
Submitted in duplicate

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone 973 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC



January 5, 2000

Charles Ganley, MD, Director
Division of Over-the Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: Request for Waiver of Pediatric Study Requirements

Dear Dr. Ganley:

Please refer to our New Drug Application (#21-076) for Aleve Cold & Sinus that was approved on November 29, 1999.

In accordance with 21 CFR 314.55 (c) (2) (i and iii) we are requesting a full waiver of the pediatric study requirements. The following describes our reasons for requesting this waiver:

- *This product does not offer a significant therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients.* Already available in the marketplace are several products that contain a pain reliever/fever reducer and a nasal decongestant [i.e. Infants' Tylenol Cold (ages 2-3), Children's Tylenol Sinus (ages 2-11)] which will have predictably comparable efficacy. In addition, the Aleve Cold & Sinus caplet contains more pseudoephedrine (120-mg over 12 hours) than is recommended for use in patients under the age of 12.

- *There is evidence strongly suggesting that this drug product would be unsafe in all pediatric age groups.* The monograph for oral nasal decongestants [21 CFR 341.80 (d) (1) (ii)] indicates that children aged 6 to under-12 should receive 30 mg of pseudoephedrine every 4-6 hours not to exceed 120 mg in 24 hours. As Aleve Cold & Sinus delivers 120 mg of pseudoephedrine over a 12-hour period, this drug product would be inappropriate for use in any child under the age of 12. In addition, the sustained release nature of the caplets prevents them from being divided into appropriate dosages for pediatric patients.

ORIGINAL

The product labeling currently states, "Do not give this product to children under 12 unless directed by a doctor."

If there be any additional requests regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

Craig Hammes
Director, Regulatory Affairs

Submitted in duplicate

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P O Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA 21-076 001
NDA SUPPL FOR SLR

January 5, 2000

NDA No. 21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

Charles Ganley, MD
Director
Division of OTC Drug Products (HFD-560)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Building 2, 2nd Floor
Document Control Room N-115
Rockville, Maryland 20850

Subject: Labeling Supplement
Expedited Review Requested
Proposed Pouch/Consumer Card/Professional Dispenser Box

Dear Dr. Ganley:

Please refer to our New Drug Application (#21-076) for Aleve® Cold & Sinus (approved November 29, 1999) and to Agency labeling comments dated November 15, 1999. The 1-count non-saleable pouch, consumer card and professional dispenser box were not part of NDA approval on November 29, 1999. Appended to this submission are mock-ups of our proposed pouch, consumer card and dispenser box for Agency review. The labeling format and content of the three components is exactly as approved for the 10-count carton, 20-count carton and consumer insert leaflet. Appended please find the following:

- 1-count non-saleable pouch with abbreviated labeling
- Direct distribution consumer "card" with full Drug Facts labeling
- Professional dispenser box with full Drug Facts labeling

ORIGINAL

During teleconferences between Bayer and Agency from November 17 through November 23, 1999, Bayer requested that this Supplement be given expedited review and we understood that FDA was agreeable to this request. If there are any questions regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Karen Mancuso for

Craig Hammes
Director,
Regulatory Affairs

Submitted in duplicate
Desk copies: Marina Chang (HFD-560)
Cazemiro Martin (HFD-560)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910

DEC 3 1999

Attention: Craig E. Hammes
Director Regulatory Affairs

Subject: Aleve Cold/Sinus (naproxen sodium/pseudoephedrine HCL)
NDA 21-076

Dear Mr. Hammes:

We received your August 18, 1999, letter regarding your August 9, 1999, telephone conversation with Eric B. Sheinin, Ph.D, Director, Office of New Drug Chemistry. In this telephone conversation, information was discussed about handling a change in the synthesis process of the key intermediate for pseudoephedrine hydrochloride drug substance. We have reviewed the information regarding this issue and agree to the following:

1. New drug applicants referencing [redacted] updated DMF for ephedrine hydrochloride and/or pseudoephedrine hydrochloride or sulfate should submit Changes Being Effected in 30 Days (CBE-30) supplements to their respective, approved New Drug Applications (NDAs). A commitment to conduct stability study on the first batch of the drug product post-approval should be included in such CBE-30 supplements, and stability data should be submitted in the annual reports.

2. For applicants with pending original NDAs, the change may be submitted as amendments to the NDAs.

Also, please attach a copy of this correspondence when you submit a CBE-30 supplement or amendment and annual report to the affected NDA(s).

If you have any further questions, please do not hesitate to contact Susan Lange, Consumer Safety Officer, Office of New Drug Chemistry at (301) 827-5915.

Sincerely,

Yuan-yuan Chiu, Ph.D.
Acting Director
Office of New Drug Chemistry
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ORIGINAL

Bayer

ORIG AMENDMENT

BL

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium and pseudoephedrine hydrochloride extended-release tablets, 220 mg/120 mg)

November 18, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: Amendment to Pending NDA
Additional Labeling Information

Dear Dr. Midthun:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and to Agency labeling comments received on November 15, 1999. Reference is also made to the labeling teleconference on November 17, 1999 between Bayer and Agency. Following the teleconference, Sharon Schmidt (HFD-550) requested additional labeling information. Provided below is the information that was faxed to Sharon Schmidt on November 18, 1999 per her request:

1. Following is our justification for the inclusion of the word "sinus" in the temporarily relieves statement under the "**Uses**" section.

   Bayer is in agreement that the words "sinus condition" in the temporarily relieves statement may imply sinusitis or a sinus infection. We are proposing the following:

   Uses temporarily relieves these cold, sinus and flu symptoms

   This "**Uses**" statement is followed immediately by the bullet point "nasal and sinus congestion...". In this way, removing the word "condition" the phrase clearly implies that the product is intended to relieve sinus symptoms such as nasal and sinus congestion, and sinus pressure, and does not imply sinusitis or sinus infection.

2. Regarding the addition of the bulleted statement under the subheading "Ask a doctor or pharmacist before use if you are", we propose the following statement:

   - using any other product containing naproxen or pseudoephedrine

   The above bullet will be placed under the 1st bulleted statement.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Craig Hammes
Director,
Regulatory Affairs

Attachments
Submitted in duplicate

Bayer

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

November 24, 1999

Sharon Schmidt, Project Leader
Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Room N362
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: Labeling

Dear Ms. Schmidt:

Included in this submission please find copies of the 10- and 20-count cartons, blister back, and consumer insert labeling. These items reflect all changes requested by FDA in our discussions from November 17th, 1999 through November 23rd, 1999.

The sample pouch, along with the "card" package for consumer sample pouches and "dispenser" box for professional sample pouches will be submitted when available as a labeling supplement as agreed.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

Craig Hammes
Director, Regulatory Affairs

Submitted in duplicate + 2 desk copies

ORIGINAL

Bayer

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

November 23, 1999

N (000) BL

Sharon Schmidt, Project Leader
Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Room N362
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: Labeling

Dear Ms. Schmidt:

Included in this submission please find copies of the carton, blister back, and consumer insert labeling. The changes requested in the November 17th and 19th, 1999 conference calls have been incorporated.

As suggested by Marina Chang, we have improved the vertical alignment of the Drug Facts bullet points to the maximum extent possible, within the space limits of the package panel.

The sample pouch, along with the "card" package for consumer sample pouches and "dispenser" box for professional sample pouches will be submitted when available as a labeling supplement as agreed.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

Craig Hammes
Director, Regulatory Affairs

Submitted in duplicate

ORIGINAL

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

ORIG AMENDMENT
BL

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

November 16, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: Amendment to Pending NDA
Response to FDA Labeling Comments

Dear Dr. Midthun:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and to Agency labeling comments received on November 15, 1999. Bayer is in concurrence with a majority of the Agency's comments and recommendations. After thorough review of the labeling recommendations, Bayer respectfully requests the Agency to reconsider the following points:

1) PRODUCT LABELING
(1-count pouch, 10- and 20-count carton, consumer labeling leaflet)

"Use" Section

We propose the "**Uses**" Section be changed to the following (using interchangeable terms, bulleted statements):

Note: Highlighted text indicates proposed additions to the "**Uses**" Section

Uses temporarily relieves these cold, sinus [redacted] and flu symptoms:

- nasal and sinus congestion (promotes sinus drainage and restores freer breathing through the nose)
- sinus pressure
- headache
- minor body aches and pains
- fever

Bayer offers the following comments regarding the above-proposed additions to the "Uses" section:

Sinus Condition

We believe it would be confusing to consumers if the words [redacted] were not included in the "**Uses**" statement. The product's tradename specifically states that the product is indicated for cold and sinus condition symptoms, therefore, the "**Uses**" section should indicate that it "temporarily relieves these cold, sinus[redacted] and flu symptoms".

Sinus Drainage & Sinus Pressure

Reference is made to 21 CFR §341.80(b)(2)(iv) and (b)(2)(v), and to the Final Monograph for OTC Nasal Decongestant Drug Products (dated August 23, 1994) which support the following indication for use terms:

[redacted]

We believe that the indications "promotes sinus drainage" [redacted] should be included under the "**Uses**" Section. Oral decongestants such as pseudoephedrine have been shown to reduce mucosal blood flow, decrease tissue edema and nasal resistance and enhance drainage of secretions from the sinus ostia mediated by alpha-adrenergic stimulation. The pharmacological activity of pseudoephedrine results in a reduction of sinus pressure and congestion while promoting sinus drainage and should be so indicated on the product labeling.

Consumers suffering from a cold, sinus condition or the flu identify congestion and sinus pressure as bothersome symptoms and utilize pseudoephedrine-containing brands as treatment. In a 1997 Cold/Sinus/Flu market research study conducted by Bayer, consumers unprompted mentions of symptoms most often experienced when suffering from a cold, sinus condition or the flu included stuffy nose/congestion (52-53%) and sinus pain/pressure (45%). In the same study, 73-77% of consumer's suffering from a cold or sinus condition noted that sinus congestion and pressure were extremely bothersome.

A review of labeling for currently marketed pseudoephedrine containing products (both NDA and monograph) underscores the historical precedents supporting the indications "temporarily relief of sinus pressure" and "promotes sinus drainage". For consumers to successfully diagnose and self-medicate with OTC drugs, we believe the inclusion of [redacted] is crucial to ensure that consumers best select the appropriate product. Consequently, consumers will be looking for these indications on our carton, as they appear in the carton labeling for virtually all currently marketed pseudoephedrine-containing products.

"Other information" Section

We have incorporated the following statement under the "Other information" section of labeling at the request of the chemistry review staff during a October 19, 1999 teleconference between Bayer and Agency:

- store in a dry place

2) PROMOTIONAL STATEMENTS ON PRINCIPAL DISPLAY PANEL (PDP)

In our prior correspondence of August 26, 1999, we submitted a draft proposed PDP. Provided below is our proposed draft PDP promotional information statements which is consistent with our proposed "**Uses**" section above.

ALL DAY RELIEF [redacted]

- Nasal Congestion and Sinus Pressure
  Plus Headache and Body Aches
- Non-Drowsy
- 1 Caplet Every 12 Hours (added as visual around pill)

The attached draft mock-up of the proposed PDP reflects the proposed promotional information statements, and also shows in mark-up, the further changes to be made to conform to the FDA comments regarding the PDP.

3) BLISTER BACK LABELING

Because of space limitations, Bayer proposes replacing hydrochloride with the chemical symbol (HCl) on the blister back.

4) PROPOSED POUCHES

We are currently preparing mock-up labeling for (a) the direct distribution card, (b) the non-saleable pouch, and (3) the dispenser boxes, and will forward copies to Agency as soon as they become available.

We look forward to the scheduled teleconference at 10:30 am on November 17th to discuss the above issues. If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Craig Hammes

Craig Hammes
Director,
Regulatory Affairs

Attachments
Submitted in duplicate

Bayer

ORIG AMENDMENT

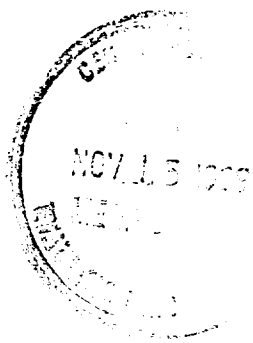
NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

November 12, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



SUBJECT: AMENDMENT TO PENDING NDA
PROCEDURE FOR SAMPLING

Dear Dr. Midthun:

Reference is made to NDA 21-076 for Aleve Cold and Sinus that was submitted on January 29th, 1999.

Provided, in duplicate, are copies of the sampling procedures for release and stability.

Provided, under separate cover, to the FDA New Jersey and San Juan District Offices, are field copies of this submission. Bayer certifies that the field copies are true copies of the information contained in the archival and review copies of this submission.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

William R. Walsh for

Craig Hammes
Director, Regulatory Affairs

Submitted in duplicate

ORIGINAL

Bayer

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

NC

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

November 8, 1999

Wayne T. Smith
Food and Drug Administration
US Customhouse, Room 900
Second and Chestnut Streets
Philadelphia, PA 19106

SUBJECT: Method Validation Studies- Supplemental Information

Dear Mr. Smith:

Reference is made to NDA 21-076 for Aleve Cold and Sinus that was submitted on January 29th, 1999. In addition, reference is made to the Methods Validation Package that was submitted to the NDA on October 11, 1999.

No changes have been made to the methods since the Methods Validation Package referenced above was submitted. That package also contains the appropriate [redacted] for the reference and impurity standards.

Included in this submission are the applicable worksheets used to test the lot of product submitted for your evaluation. The worksheets for the 12-month time point stability data were generated using the most current methods provided in the Methods Validation Package.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

Craig Hammes

Craig Hammes
Director, Regulatory Affairs

cc: FDA- San Juan Laboratory (+ samples)
In duplicate to FDA NDA files (document only)

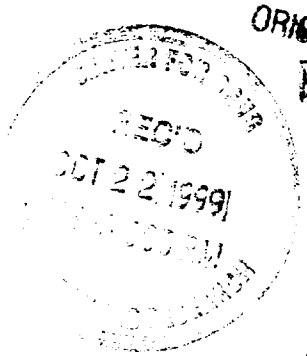
Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone 973 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

ORIG AMENDMENT
BC



October 20, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Item #1 of this Phase IV Commitment is acceptable to DPE III.
/s/ 11/19/99

SUBJECT: AMENDMENT TO THE NDA: PHASE IV CMC COMMITMENTS

Dear Dr. Midthun:

Reference is made to NDA 21-076 for Aleve Cold and Sinus that was submitted on January 29th, 1999. Reference is also made to the Agency's request for additional CMC information made to Bayer via phone conversation on October 19th, 1999, and the phone conversation between Sue Ching Lin (FDA) and Bayer (Craig Hammes and Bill Walsh) on October 20, 1999.

Bayer commits to submit the following information within one year of the product approval date:

1. Bayer will modify the product dissolution method and specifications to better reflect the product's *in vivo* performance. The information will be submitted as a Prior Approval Supplement.

2. Bayer will re-evaluate the Loss on Drying specification (% LOD) for the finished product using the new dissolution method (see above #1) and accumulated long term stability data. The current specification will remain at [redacted] until further data is submitted. The data will be submitted as a Prior Approval Supplement.

ORIGINA

As per FDA's request, attached as Appendix I are the individual tablet dissolution results from [redacted]

Bayer will comply with FDA's request that "Store in a dry place" be added to the product labeling. The change will be reflected in the final printed labeling.

Provided, under separate cover, to the FDA New Jersey and San Juan District Offices, are field copies of this submission. Bayer certifies that the field copies are true copies of the information contained in the archival and review copies of this submission.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

Craig Hammes
Director, Regulatory Affairs

Submitted in duplicate

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

ORIG AMENDMENT

EM

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

October 19, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: Response to FDA Request for Information
Study No. S97-052 Supplemental Tables

Dear Dr. Midthun:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and to Sharon Schmidt's request of October 15, 1999 regarding additional analysis for Study No. S97-052 (Natural Cold Study). Provided with this correspondence are the following tables:

- Table P-6 Supplemental entitled "Morning Symptom Evaluation Analysis (Primary Efficacy Subjects) (All Sites Pooled, Baseline Nasal Obstruction Moderate to Severe"
- Table P-8 Supplemental entitled "By Hour Analyses of Nasal Obstruction for Days 1 and 2 (Primary Efficacy Subjects) (All Sites Pooled, Baseline Nasal Obstruction Moderate to Severe)

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Craig Hammes
Director,
Regulatory Affairs

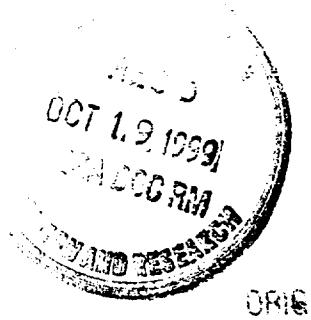
Attachment
Submitted in duplicate

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC



ORIG AMENDMENT

BC

October 18, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: GENERAL CORESPONDENCE
RESPONSE TO CMC INQUIRY-
JUSTIFICATION OF % LOSS ON DRYING SPECIFICATION

Dear Dr. Midthun:

Reference is made to NDA 21-076 for Aleve Cold and Sinus that was submitted on January 29th, 1999. Reference is also made to the Agency's request for additional CMC information received by Bayer on October 13th, 1999.

Provided, in duplicate, is a copy of the report justifying the % Loss on Drying limit [redacted] set by Bayer in the product specifications.

Provided, under separate cover, to the FDA New Jersey and San Juan District Offices, are field copies of this submission. Bayer certifies that the field copies are true copies of the information contained in the archival and review copies of this submission.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

Craig Hammes
Director, Regulatory Affairs

Submitted in duplicate

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

October 12, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: Response to FDA Request
Fever Data for Study Nos. S97-051 and S97-052

Dear Dr. Midthun:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and to Sharon Schmidt's request for fever data for the natural and induced cold studies (Study Nos. S97-052 and S97-051, respectively). Body temperature was measured in the induced cold trial (S97-051) only. Increased body temperatures were not expected to be seen in this model and temperatures were only measured as a record of vital signs. Appended please find an executive summary as well as an analysis of the oral temperature data collected in Study S97-051.

While body temperature was not measured in Study S97-052, chilliness was assessed by subject and analyzed for both studies (S97-051 and S97-052). Based upon the chilliness data we can predict that fever was mostly absent amongst the naturally occurring cold population as it was in the induced cold population. The following pages can be referred to in the original NDA submission regarding an analysis of chilliness for both final study reports:

	Vol.	Page No.
Study S97-051 (Induced Cold)		
Baseline Chilliness	20	59
Morning Symptom Evaluation Analysis (primary efficacy subjects)	20	69
Repeated Measures Analysis of Chilliness (primary efficacy subjects)	20	97
Morning Symptom Evaluation of Analysis (intent to treat)	20	117
Repeated Measures Analysis of Chilliness (intent to treat)	20	115

	Vol.	Page No.
Study S97-052 (Natural Cold)		
Baseline Chilliness (primary efficacy subjects)	23	52
Morning Symptom Evaluation Analysis (primary efficacy subjects)	23	58
Repeated Measures Analysis of Chilliness (primary efficacy subjects)	23	92
Morning Symptom Evaluation Analysis (intent to treat)	23	108
Repeated Measures Analysis of Chilliness (intent to treat)	23	106

Reference is also made to the New Drug Application #20-204 for Aleve® (naproxen sodium, 220 mg) OTC submitted on April 15, 1992. A study (#1683) to assess the fever reducing ability of naproxen was conducted and submitted in the original submission of NDA #20-204. Appended please find the Study Synopsis and Final Study Report with Tables and Figures for Study No. 1683 entitled "A Double-Blind Evaluation of the Antipyretic Effect of Naproxen in Endotoxin-Induced Fever". This fever study demonstrated that both the 200mg and 400 mg doses of naproxen were effective fever reducers. Please note that 200 mg of naproxen is equivalent to 220 mg naproxen sodium.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Karen M Mancuso for

Craig Hammes
Director,
Regulatory Affairs

Attachment
Submitted in duplicate
Desk copy: Christina Fang, Medical Officer (HFD-550)

ORIGINAL

Bayer

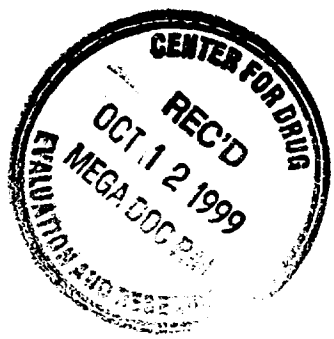
Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, N.J. 07962-1910
Phone: 201 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

ORIG AMENDMENT

BC



October 11, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: GENERAL CORESPONDENCE
METHODS VALIDATION PACKAGE

Dear Dr. Midthun:

Reference is made to NDA 21-076 for Aleve Cold and Sinus that was submitted on January 29th, 1999, and to the request for information from the Agency received by Bayer on September 21st, 1999.

Provided are four copies of methods validation package as requested in the 9/21/99 memo to Bayer. These packages include the following information:

1. Tabular listing of all samples to be submitted
2. Statement of Composition and Product Specifications
3. Test Methods
4. Method Validation Reports
5. MSDS's for Reference Standards
6. Reference Material Certificates of Analysis

Bayer will provide the samples to the FDA-designated testing laboratories upon receipt of their names and addresses from the review chemist.

Provided, under separate cover, to the FDA New Jersey and San Juan District Offices, are field copies of this submission. Bayer certifies that the field copies are true copies of the information contained in the archival and review copies of this submission.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

William R. Walsh /for

Craig Hammes
Director, Regulatory Affairs

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

ORIG AMENDMENT

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

BC

October 11, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: GENERAL CORESPONDENCE
RESPONSES TO CMC INQUIRIES

Dear Dr. Midthun:

Reference is made to NDA 21-076 for Aleve Cold and Sinus that was submitted on January 29th, 1999.

Provided, in duplicate, are copies of Bayer's responses to the FDA's request for additional chemistry information. Bayer received the request on September 21st, 1999. Also included is a copy of the lab-to-lab degradation method transfer report that was cited as a deficiency in the 483 issued to [redacted]

It is our understanding that this information, along with the 12-month stability data that was submitted on 10/4/99, will satisfy the outstanding requests from the San Juan District office and will support a recommendation for approval of the intended production facility [redacted]

Provided, under separate cover, to the FDA New Jersey and San Juan District Offices, are field copies of this submission. Bayer certifies that the field copies are true copies of the information contained in the archival and review copies of this submission.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4793 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

William R Walsh/for

Craig Hammes
Director, Regulatory Affairs

Submitted in duplicate

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, N.J. 07962-1910
Phone: 201 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

October 4, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: AMENDMENT TO PENDING NDA
12-MONTH STABILITY DATA UPDATE

Dear Dr. Midthun:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999. In accordance with our commitment please find the 12-month stability data for this product.

Provided, under separate cover, to the FDA New Jersey District Office and the FDA San Juan District Office, are field copies of this submission. Bayer certifies that all the copies are true copies of the information contained in the archival and review copies of this submission.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

Rich Cuprys
Associate Director,
Regulatory Affairs

ORIGINAL

Submitted in duplicate

ORIG AMENDMENT

ORIGINAL

BC

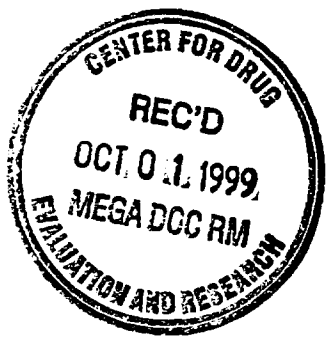
Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220mg and pseudoephedrine hydrochloride 120 mg) OTC

September 30, 1999



Karen Midthun, MD. Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
ATTN: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: General Correspondence
NDA Commitment - Chemistry, Manufacturing, and Controls

Dear Dr. Midthun:

Please refer to our pending New Drug Application (#21-076) for naproxen sodium, 220 mg and pseudoephedrine HCl, 120 mg, sponsored by Bayer Corporation (Bayer), Consumer Care Division. Reference is also made to a discussion between Dr. Amit Mitra, Sue-Ching Lin. Sharon Schmidt, and Rich Cuprys (Bayer) on September 21, 1999 related to the pseudoephedrine HCl used in the manufacture of the subject drug product.

Our supplier [redacted] of pseudoephedrine HCl recently submitted to the Agency a fully revised update of their drug master file [redacted] to reflect a change in the synthesis process of the key intermediate, ephedrine HCl. [redacted] nformed Bayer that they had detailed discussions with the Agency regarding this change. Based on these discussions, the Agency has outlined regulatory obligations whereby applicants referring to the updated DMF will be able to submit supplemental applications for the change with release data on one batch of drug product with a post approval stability commitment for the first production batch. A recent telephone discussion between Dr. Eric Sheinin (Director, Office of New Drug Chemistry) and Craig Hammes (Bayer) confirmed that the supplemental application plan as outlined above will be acceptable for the subject NDA drug product.

Karen Midthun, MD
NDA #21-076

September 30, 1999

Subsequent to the approval of the subject NDA, Bayer plans to submit a supplemental application pursuant to 21 CFR 314.70(b) that will provide for the use of pseudoephedrine HCl made by the new synthesis process. Due to the discontinuation of material made by the current process, and very limited stockpiles of the active ingredient, Bayer will request for expedited review of the supplemental application.

As requested at the referenced discussion, Bayer commits to the continued use of pseudoephedrine HCl made by the current process as described in the pending NDA, and will not introduce into the marketplace drug product made with the new process pseudoephedrine until approval of the supplemental application.

Sincerely,
Bayer Corporation
Consumer Care Division

Rich Cuprys
Associate Director,
Regulatory Affairs

Submitted in duplicate
Desk Copy: Sue-Ching Ling (HFD-550)

DUPLICATE

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NEW CORRESP

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

September 21, 1999

Karen Midthun, MD, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: General Correspondence: Meeting Minutes from June 29, 1999 FDA/Bayer Teleconference

Dear Dr. Midthun:

Reference is made to our New Drug Application (#21-076) for naproxen sodium 220 mg and pseudoephedrine HCl 120 mg, submitted by Bayer Corporation, Consumer Care Division on January 28,1999. Reference is also made to an e-mail from Karen Mancuso to Sharon Schmidt dated July 8, 1999 forwarding draft meeting minutes from the June 29, 1999 teleconference and to Sharon Schmidt's fax of July 14, 1999 providing the team's comments. We have incorporated the team's comments into the meeting minutes. Appended please find the final meeting minutes to the June 29, 1999 teleconference.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Karen M Mancuso for

Rich Cuprys
Associate Director,
Regulatory Affairs

Attachment
Submitted in duplicate

ORIGINAL

BM

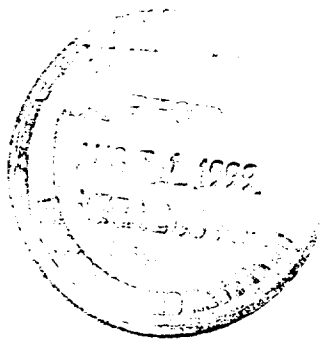
Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA #21-076
Aleve Cold & Sinus
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

NDA ORIG AMENDMENT



August 30, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
ATTN: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Subject: **General Correspondence -**
Response to FDA Safety Data Request of 8/25/99

Dear Dr. Midthun:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and to an email communication from Dr. Christina Fang (HFD-550) received on 8/25/99 requesting additional subject safety information related to naproxen sodium overdose. Appended please find the original table provided by Dr. Fang with available information presented in bold. In addition, we are providing the extended summary reports for each of the subjects identified in the table. We trust this is responsive to Dr. Fang's request.

If there are any questions or comments regarding this submission please contact the undersigned at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Rich Cuprys
Associate Director
Regulatory Affairs

Attachment
Submitted in duplicate

ORIGINAL

Bayer

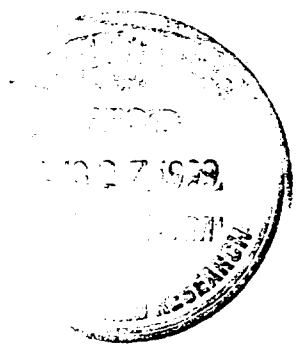
Consumer Care Division

Bayer Corporation
36 Columbia Road
P O Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

ORIG AMENDMENT

BL

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC



August 26, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: General Correspondence: Proposed Principal Display Panel
Minor Editorial Changes in Draft Labeling

Dear Dr. Midthun:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999. Appended please find revised principal display panels for the 10- and 20-count cartons for your review. Also, as a result of the July 19, 1999 teleconference with Sharon Schmidt, Cazemiro Martin, Marina Chang and representatives from Bayer, the following minor editorial changes have been made to the draft labeling:

- Active ingredients section: "extended release" was added after pseudoephedrine hydrochloride 120 mg
- Two changes were made in the Directions section: 1) Do not crush or chew, swallow whole was changed to "Swallow whole: Do not crush or chew," 2) The adults category was changed to "Adults and children 12 years of age and older."

We look forward to your comments on our proposed principal display panel at your earliest convenience. If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Karen A M Jancuso for

Rich Cuprys
Associate Director,
Regulatory Affairs

Attachment
Submitted in duplicate
Desk copies: Cazemiro Martin (HFD-560)
Marina Chang (HFD-560)

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, N.J. 07962-1910
Phone: 201 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

August 18, 1999

ORIG NEW CORRES
NC

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: Response to FDA Request for Information: Information to Support the Safety Update

Dear Dr. Midthun:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and our Safety Update submitted on July 13, 1999. Reference is also made to a telephone conversation between Sharon Schmidt (HFD-550) and Karen Mancuso (Bayer) on Friday, July 23, 1999 regarding Dr. Christina Fang's request for additional information to support the Safety Update. Appended please find an Executive Summary of all safety issues discussed in the Safety Update per Dr. Christina Fang's request.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

William R. Walsh for

Rich Cuprys
Associate Director,
Regulatory Affairs

Attachment
Submitted in duplicate

ORIGINAL

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, N.J. 07962-1910
Phone: 201 254-5000

NEW CORRESP
NC

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

AUG 17 1999

August 16, 1999

Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Noted
Will be reviewed by the division
thereon

8/20/99

SUBJECT: GENERAL CORESPONDANCE
RESPONSES TO FDA 483

Dear Dr. Midthun:

Reference is made to NDA 21-076 for Aleve Cold and Sinus that was submitted on January 29th, 1999.

Provided, in duplicate, are copies of the companies' responses to the FDA 483 that was issued on July 23, 1999. The FDA 483 was issued to the [redacted] plant located in [redacted] which is the intended site of manufacturing. The responses to the FDA 483 were hand delivered to the San Juan District office on August 10th, 1999.

Only the responses to observations pertaining to Aleve Cold and Sinus (No. 1-5) are contained in this submission. Bayer certifies that the copies are true copies of the information provided to the San Juan District office.

Provided, under separate cover, to the FDA New Jersey District Office, is a field copy of this submission. Bayer certifies that the field copy is a true copy of the information contained in the archival and review copies of this submission.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Bill Walsh at (973) 408-8046

Sincerely,
Bayer Corporation
Consumer Care Division

William R. Walsh for

Rich Cuprys
Associate Director,
Regulatory Affairs

Submitted in duplicate

ORIGINAL
NC

Bayer

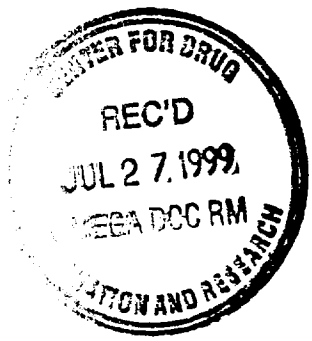
Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

July 26, 1999

NEW CORRESP



Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: ADDENDUM TO ENVIRONMENTAL ASSESSMENT

Dear Dr. DeLap:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and to a request from Nancy Sager (HFD-357) of July 26, 1999 requesting additional information to support the environmental assessment. Provided in this submission is the following information:

- Identification information for pseudoephedrine hydrochloride
- Justification for not providing full information on the pseudoephedrine component

Provided, under separate cover, to the FDA New Jersey District Office and the FDA San Juan District Office are field copies of this submission. Bayer certifies that the field copies are true copies of the information contained in the archival and review copies of this submission.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Rich Cuprys
Associate Director,
Regulatory Affairs

Attachment
Submitted in duplicate
Desk copy: Nancy Sager (HFD-357)

ORIG AMENDMENT

ORIGINAL

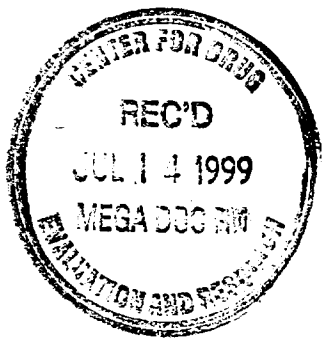
Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P O Box 1910
Morristown, NJ 07962-1910
Phone 973 254-5000

NDA #21-076
ALEVE COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

July 13, 1999



Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: AMENDMENT TO A PENDING NEW DRUG APPLICATION
SAFETY UPDATE

Dear Dr. DeLap:

Reference is made to our pending New Drug Application (#21-076) for Aleve Cold & Sinus (naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) dated January 28, 1999 where Bayer Consumer Care (Bayer) committed to the following:

- Submit an integrated summary of information about the safety of the individual ingredients obtained from the World Health Organization (WHO) database in a Safety Update Report

- Search and monitor a variety of sources for additional safety data related to the individual ingredients naproxen sodium, and pseudoephedrine hydrochloride, and for any available information on the combination of the ingredients

Bayer Consumer Care is herewith amending this pending application to provide the required update of safety data. The attached update provides the following safety data:

- Safety information obtained from the literature for the period of January 1999 to June 1999
- Information received from serious spontaneous reports on OTC naproxen sodium from January 1999 to May 1999
- Information from the WHO database for adverse events reported from January 1994 to June 16, 1999

These additional data confirm that the safety profiles of naproxen sodium and pseudoephedrine hydrochloride are well-characterized and provide adequate support for the safe nonprescription use of the combination product. In addition, there are no newly emerging adverse experiences not previously known. Therefore, there is no additional information that would change the proposed product labeling as submitted in the NDA.

Should you have any questions or need additional information, please feel free to contact the undersigned at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Rich Cuprys
Associate Director,
Regulatory Affairs

/Attachments
Submitted in duplicate
Desk copy: Christina Fang, Medical Officer (HFD-550)

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, N.J. 07962-1910
Phone: 201 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

July 13, 1999

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: AMENDMENT TO PENDING NDA
CHEMISTRY, MANUFACTURING & CONTROLS

Dear Dr. DeLap:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999. In accordance with our commitment (see memo from Bayer to Lin and Rosa dated 5/12/99) we are enclosing the following information:

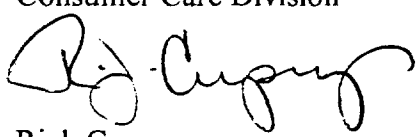
1) Revalidation of the degradation products assay to include the degradation products of pseudoephedrine HCl
2) The analytical methods and methods validation re-formatted to comply with the FDA guidance
3) [redacted]
4) [redacted]

At the request of the review chemist, Bayer agrees to withdraw the packaging equivalency protocol from consideration. Bayer will submit any proposed packaging material changes as a post-approval Prior-Approval supplement. In addition, the dissolution specifications for pseudoephedrine HCl at 3 hours have been revised to better reflect USP guidelines. Also included is a diskette that contains Word 97 versions of the product specifications and a sample of the stability protocol. (All files were virus scanned.)

Provided, under separate cover, to the FDA New Jersey District Office and the FDA San Juan District Office, are field copies of this submission. In addition, two copies of the methods validation package have been forwarded to the review chemist under separate cover. Bayer certifies that all the copies are true copies of the information contained in the archival and review copies of this submission.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division



Rich Cuprys
Associate Director,
Regulatory Affairs

Submitted in duplicate

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NEW CORRESP
NC hl please

NDA #21-076
ALEVE COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

June 11, 1999

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: GENERAL CORRESPONDENCE: Revised Carton Layouts

Dear Dr. DeLap:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and to our General Correspondence/Background Package for Draft Labeling Meeting submitted on March 21. 1999. Reference is also made to a telecon on May 26, 1999 between Cazemiro Martin, Marina Chang, Sharon Schmidt (FDA), and Rich Cuprys and Karen Mancuso (Bayer). During the May 26th telecon, Cazemiro Martin indicated that the 2-column format that was submitted on May 21st is not provided in the final rule and that Bayer should submit carton layouts (10's and 20's) in a 1-column format. Appended please find the following labeling:

- 10-Count Carton (1-column layout)
- 20-Count Carton (1-column layout)

The following changes were also made to the labeling as a result of the May 26th teleconference:

- A question mark was added at the end of the "Questions or comments" statement
- The asterisk following the word "caplets" was retained on the principal display panel and removed from the back and side panels.
- The bolding in the pregnancy warning was removed (except for the first 4 words) and the text was changed from upper case to lower case.
- The sodium content statement under "Other information" was changed to: ***Other Information*** • Each caplet contains: sodium 20 mg.

ORIGINAL

Should you have any questions or need additional information, please feel free to contact the undersigned at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Karen T Mancuso for:

Rich Cuprys
Associate Director,
Regulatory Affairs

/Attachments
Submitted in duplicate
Desk copies: Cazemiro Martin (HFD-560)
Marina Chang (HFD-560)

ORIGINAL

EC

Bayer

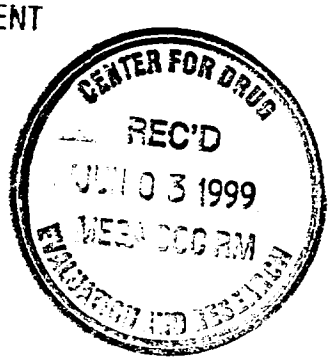
Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA #21-076
Aleve® Cold and Sinus
(naproxen sodium 220 mg and
pseudoephedrine HCl 120 mg) OTC

June 2, 1999

ORIG AMENDMENT



Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: General Correspondence
Addressing of CMC Issues

Reference is made to NDA#21-076 for naproxen sodium 220 mg and pseudoephedrine HCl 120 mg, submitted by Bayer Corporation, Consumer Care Division, on January 28, 1999 and the meeting minutes from the April 28th, 1999 conference call, which were submitted to the NDA on May 6th, 1999.

Attached please find Bayer's updated response to issues that were discussed in the April 28th, 1999 conference call. For each item we have included the original FDA request, Bayer's written response prior to the conference call, a summary of the discussion that took place during the conference call, and an update on the status of the request.

Provided, under separate cover, are field copies of this submission addressed to the San Juan and New Jersey District Offices, as well as a copy to Dr. Dennis Bashaw (HFD-880). Bayer certifies that the field copies are true copies of this submission.

If you have any questions or need additional information, please feel free to contact me at (973) 254-4673 or in my absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

William R Walsh for

Rich Cuprys
Associate Director, Regulatory Affairs

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone 973 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

[redacted]

BL

May 28, 1999

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: GENERAL CORRESPONDENCE: ELECTRONIC FILE OF DRAFT LABELING

Dear Dr. DeLap;

Pursuant to Cazemiro Martin's request of May 26, 1999, enclosed please find a diskette with the Aleve Cold & Sinus labeling in Microsoft Word. The diskette has been virus scanned using McAfee VirusScan NT.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Karen Mancuso for

Rich Cuprys
Associate Director,
Regulatory Affairs

/kam
Submitted in duplicate
Desk copy: Cazemiro Martin (HFD-560) with 2 sample blank boxes

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P O Box 1910
Morristown, NJ 07962-1910
Phone 973 254-5000

NDA #21-076
ALEVE COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

May 21, 1999

CDER AMENDMENT

BL

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: GENERAL CORRESPONDENCE: BACKGROUND PACKAGE FOR DRAFT LABELING MEETING

Dear Dr. DeLap:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and to the Drug Facts Labeling Final Rule published March 17, 1999. Provided with this correspondence are four (4) copies of draft labeling for ALEVE COLD & SINUS (naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC. The 10-count carton, 20-count carton, and 1-count pouch labeling has been revised by incorporating drug facts labeling format. Appended please find 4 copies of the following labeling:

- 1 count Pouch (Full Labeling)
- 10-Count Carton (Full Labeling)
- 20-Count Carton (Full Labeling)
- Consumer Labeling Leaflet (Full Labeling)
- Blister Back

Reference is made to our General Correspondence submission dated March 16, 1999 requesting a meeting to discuss labeling issues for Aleve Cold & Sinus. The purpose of this meeting is to initiate discussions related to the format and content of the appended draft labeling, product uses, and the principal display panel. Bayer would be available for a meeting during the weeks of June 7, 1999 and June 14, 1999. We anticipate participants from HFD-550 and HFD-560. The following is a list of Bayer representatives planning to attend the meeting:

Mr. Craig Hammes, Director, Regulatory Affairs
Mr. Rich Cuprys, Associate Director, Regulatory Affairs
Ms. Karen Mancuso, Manager, Regulatory Affairs
Mr. William Walsh, Senior Regulatory Associate, Regulatory Affairs
Mr. Joseph Repko, Graphics Project Specialist, Package Graphics

We look forward to your prompt response to this request and to the scheduling of the meeting. Bayer will follow-up to confirm meeting logistics within the next week. Should you have any questions or need additional information, please feel free to contact the undersigned at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Karen Mancuso for

Rich Cuprys
Associate Director,
Regulatory Affairs

/Attachments
Submitted in quadruplicate
Desk copy: Sharon Schmidt (HFD-550)

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NEW CORRESP
NC

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

March 8, 1999

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: GENERAL CORRESPONDENCE:
Electronic Files for Original NDA Submission

Dear Dr. DeLap:

Reference is made to our New Drug Application (#21-076) sponsored by Bayer Corporation, Consumer Care Division, "Bayer" submitted on January 28, 1999 and to the Pre-NDA Meeting of December 16, 1998 between representatives of the Agency and Bayer. At the pre-NDA meeting, the Agency requested electronic copies of the SAS transport data sets and text of study reports. Provided with this correspondence are the following 6 diskettes:

Annotated Labeling in Microsoft Word
Draft Labeling in Microsoft Word

- Clinical Study S97-049 Text in Microsoft Word
- SAS transport data sets for Study S97-049
- Clinical Study S97-050 Text in Microsoft Word
- SAS transport data sets for Study S97-050
- Clinical Study S97-051 Text in Microsoft Word
- SAS transport data sets for Study S97-051
- Clinical Study S97-052 Text in Microsoft Word
- SAS transport data sets for Study S97-052
- Clinical Study S98-068 Text in Microsoft Word
- SAS transport data sets for Study S98-068

Also provided are hardcopy printouts identifying the contents of each diskette. Please note that all disks have been virus scanned using Network Associates VirusScan for Windows NT V4.0.2.

Should you have any questions or need additional information, please feel free to contact the undersigned at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Karen Mancuso for:

Rich Cuprys
Associate Director,
Regulatory Affairs

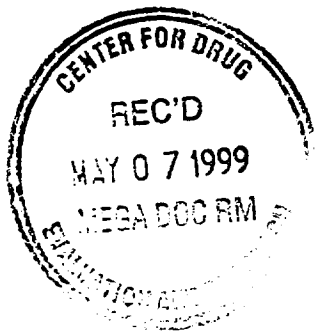
/Attachments
Submitted in duplicate

ORIGINAL **Bayer**

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA #21-076
Aleve® Cold and Sinus
(naproxen sodium 220 mg and
pseudoephedrine HCl 120 mg) OTC



May 6, 1999

NEW CORRESP

NC

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: General Correspondence
Minutes from April 28, 1999 FDA/Bayer Teleconference

Reference is made to NDA#21-076 for naproxen sodium 220 mg and pseudoephedrine HCl 120 mg, submitted by Bayer Corporation, Consumer Care Division, on January 28, 1999.

Attached please find Bayer's minutes from the subject meeting. These minutes were developed in conjunction with the FDA review chemist and project leader.

Thank you again for an effective and well-orchestrated meeting. If you have any questions or need additional information, please feel free to contact me at (973) 254-4673 or in my absence, Bill Walsh at (973) 408-8046.

Sincerely,
Bayer Corporation
Consumer Care Division

William J. Walsh for

Rich Cuprys
Associate Director
Regulatory Affairs

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 [illegible]
[illegible]town, NJ 07962-1[illegible]
Tele: 973 254-5000

Metal
C. Fine
6/3/99

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

April 28, 1999

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville. MD 20850

SUBJECT: AMENDMENT TO PENDING NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS INFORMATION

Dear Dr. DeLap:

Reference is made to our New Drug Application (#21-076) sponsored by Bayer Corporation. Consumer Care Division, "Bayer" submitted on January 28, 1999 and to Dr. Sue-Ching Lin's request for Chemistry, Manufacturing, and Controls information. Provided below is the information that was faxed to Dr. Lin on March 11th and March 12th, 1999.

All sites responsible for the manufacturing and controlling of the drug substance and drug product are prepared for pre-approval inspection.

The street addresses and CFN numbers for each site used for manufacturing and controlling of the drug substance are:

Control site for pseudoephedrine:

[redacted]

Manufacturing site for pseudoephedrine:

[redacted]

Manufacturing and Control Site for naproxen sodium

[redacted]

Following is the information that was requested regarding [redacted] acceptance of the drug substances:

Naproxen Sodium

[redacted] will perform ID tests and accept the [redacted] from the supplier. Once a year, one lot of material from quarantine will be subject to full acceptance testing.

Pseudoephedrine

[redacted] will perform full USP testing of ten lots from quarantine then move the supplier to the "reduce" testing program in which only ID is performed on the lots. Once a year, one lot of material from quarantine will be subject to full acceptance testing.

Should you have any questions or need additional information, please feel free to contact the undersigned at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Karen M Mancuso for

Rich Cuprys
Associate Director,
Regulatory Affairs

Submitted in duplicate

ORIGINAL

XR

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

April 15, 1999

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: AMENDMENT TO PENDING NDA
AMENDED PATENT CERTIFICATION

Dear Dr. DeLap:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999. In accordance with 21 CFR §314.60 we are enclosing documentation to provide for an Amendment to the Patent Certification as follows:

At the time of the original New Drug Application submission, Bayer certified that the claims of the patent pertaining to this application were invalid under 35 USC § 103 for the reasons set forth in the opinion of the Court of Appeals for the Federal Circuit.

Attached please find an Amended Patent Certification which provides for a Covenant Not to Sue

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778

Sincerely,
Bayer Corporation
Consumer Care Division

Rich Cuprys
Associate Director,
Regulatory Affairs

Submitted in duplicate

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, N.J. 07962-1910
Phone: 201 254-5000

ORIG AMENDMENT

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

April 15, 1999

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: AMENDMENT TO PENDING NDA
CHEMISTRY, MANUFACTURING & CONTROLS

Dear Dr. DeLap:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999. In accordance with 21 CFR §314.60 we are enclosing documentation to provide for the following:

[redacted]

We are supplying this data in partial fulfillment of the commitment included in the Proposed Expiration Date (section 4.2.19.) portion of the application. The testing was performed in accordance with the stability protocol included in the application (section 4.2.20.). The data to this date support the stability of this formulation. [redacted]

Also included in this amendment are several minor revisions to the stability data that was supplied in the original submission. These revisions do not affect the conclusion of the results. The product stability was within specifications at 3 months. A "Note to Reviewer" page has been included in this amendment detailing the location of the inadvertent omissions in the original NDA submission, as well as location of the corrected pages within this submission.

Provided, under separate cover, to the FDA New Jersey District Office is a field copy of this submission. Bayer certifies that the field copy is a true copy of the information contained in the archival and review copies of this submission.

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Bill Walsh at (973) 408-8046

Sincerely,
Bayer Corporation
Consumer Care Division

Rich Cuprys
Associate Director,
Regulatory Affairs

Submitted in duplicate

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

Noted
4/9/99

ORIGINAL
NC

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC

March 30, 1999

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: GENERAL CORRESPONDENCE:
INDEX FOR EACH VOLUME OF CLINICAL SECTION
OF ORIGINAL NDA

Dear Dr. DeLap:

Reference is made to our New Drug Application (#21-076) sponsored by Bayer Corporation, Consumer Care Division, "Bayer" submitted on January 28, 1999 and to Dr. Christina Fang's request of March 25, 1999. Provided with this correspondence are indexes for each volume of the Clinical Section of our original NDA (#21-076).

Should you have any questions or need additional information, please feel free to contact the undersigned at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Rich Cuprys
Associate Director,
Regulatory Affairs

/Attachments
Submitted in duplicate
cc: Sharon Schmidt (HFD-550)

NC
ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone 973 254-5000

Withdrawn
C. Fung
3/23/99

NDA #21-076
ALEVE® COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

March 16, 1999

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: GENERAL CORRESPONDENCE: REQUEST FOR MEETING

Dear Dr. DeLap:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and to our Draft Labeling submission dated March 5, 1999. Reference is also made to the Pre-NDA meeting between Bayer and Agency (December 16, 1998) where several issues concerning draft labeling were discussed. During the Pre-NDA Meeting, both Bayer and the Agency agreed that it would be beneficial to discuss and resolve all labeling issues early in the NDA process to avoid any last minute labeling issues.

This correspondence formally requests scheduling of a meeting to further discuss and reach concurrence on the following labeling issues:

- Packaging Components: Content and Format of Carton, Package Insert, Blister and Pouch
- Product Uses / Principal Display Panel
- Drug Facts Labeling Final Rule

We will provide the Agency with a complete meeting package at least two weeks prior to the scheduled meeting.

We look forward to your prompt response to this request and to the scheduling of the meeting. If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Karen Mancuso for

Rich Cuprys
Associate Director,
Regulatory Affairs

Submitted in duplicate
Desk copy: Sharon Schmidt (HFD-550)

ORIGINAL

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone 973 254-5000

NDA #21-076
ALEVE COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120 mg) OTC

March 5, 1999

Robert J. DeLap, MD, Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: GENERAL CORRESPONDENCE: DRAFT LABELING

Dear Dr. DeLap:

Please refer to our New Drug Application (#21-076) submitted on January 28, 1999 and to a fax from Sharon Schmidt (HFD-550) dated March 3, 1999 requesting draft labels for all containers. Provided with this correspondence are four (4) copies of draft labeling for ALEVE COLD & SINUS (naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg) OTC as follows:

- Carton Front Panel
- Carton Back Panel (Full Labeling)
- Blister Back
- Consumer Labeling Leaflet (Full Labeling)
- Pouch Front (Full Labeling)
- Pouch Back (Full Labeling)

If there are any questions or comments regarding this submission, please contact the undersigned by phone at (973) 254-4673 or in his absence, Karen Mancuso at (973) 254-4778.

Sincerely,
Bayer Corporation
Consumer Care Division

Rich Cuprys
Associate Director,
Regulatory Affairs

/Attachments
Submitted in quadruplicate
Desk copy: Sharon Schmidt (HFD-550)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Bayer Corporation
Attention: Rich Cuprys, Associate Director
Regulatory Affairs
Columbia Road
P.O. Box 1910
Morristown, New Jersey 07962-1910

Dear Mr. Cuprys

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Aleve Cold and Sinus (naproxen sodium, 220 mg and pseudoephedrine hydochloride, 120 mg) tablets

Therapeutic Classification: Standard (S)

Date of Application: January 28, 1999

Date of Receipt: January 29, 1999

Our Reference Number: 21-076

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 30, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 25, 1999 and the secondary user fee goal date will be January 29, 2000.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, contact Sharon Schmidt, M.S., Project Manager, at (301) 827-2536.

Sincerely,

/S/

Anthony M. Zeccola
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Archival NDA 21-076
HFD-550/Div. Files
HFD-550/S.Schmidt
DISTRICT OFFICE

Drafted by: sas/February 5, 1999
Initialed by:
final:

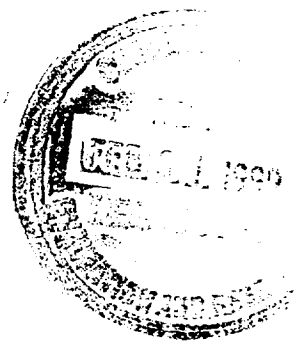
ACKNOWLEDGEMENT (AC)

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, N.J. 07962-1910
Phone: 201 254-5000

January 28, 1999



Food & Drug Administration
Center for Drug Evaluation and Research
Attn: Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

SUBJECT: ORIGINAL NEW DRUG APPLICATION # 21-076
ALEVE COLD & SINUS
(naproxen sodium, 220 mg and
pseudoephedrine hydrochloride, 120mg) OTC

Dear Sir / Madam:

Pursuant to section 505(b)(1) of the act and 21 CFR 314.50, Bayer Corporation, Consumer Care Division (Bayer) is submitting this New Drug Application (NDA) for ALEVE COLD & SINUS (naproxen sodium, 220 mg and pseudoephedrine hydrochloride, 120 mg). We also refer you to our IND [redacted] for all investigational activities and communications related to the subject product, and to the Pre-NDA meeting (12/16/98) between representatives of the Agency and Bayer.

This combination drug product is intended for non-prescription (OTC) use as a pain reliever / fever reducer / nasal decongestant. It is bi-layer tablet which combines the identical immediate-release formulation found in Aleve® (NDA # 20-204) with a sustained-release matrix formula of pseudoephedrine hydrochloride similar to a number of commercially available OTC products.

A significant body of information exists for the individual components of this combination drug product. The active ingredients are well characterized and well documented from a technical perspective, and both clinically and phamacokinetically.

The safety and efficacy for ALEVE COLD & SINUS is supported by two adequate and well-controlled trials conducted in patients with both induced and naturally-occurring colds. The primary efficacy variable designated in the clinical protocols was nasal obstruction, with an important secondary objective of evaluating the effectiveness of the active treatment in reducing the systemic cold symptoms of headache pain and malaise. Accordingly, we are requesting three-year marketing exclusivity from the date of approval of this application under the provisions of 21 CFR 314.108(b)(4) based on these new clinical investigations that are essential for approval.

Our clinical program also included three bioavailability / bioequivalency trials. One study was conducted to determine food effects, the second trial compared the drug product to its individual components, and the third study compared the product utilized in our clinical trials to the proposed commercially manufactured product. As recommended by the Agency, the nonclinical program included a bacterial reverse mutation assay, and a developmental toxicity study in one species. Further, the NDA includes safety summary data from scientific literature and post-marketing surveillance related to the individual active ingredients.

The proposed labeling for ALEVE COLD & SINUS follows Drug Facts format. The labeling content incorporates labeling statements approved for ALEVE as well as statements that appear in the final monograph for OTC nasal decongestant drug products. Included in this application are the results from our label comprehension study.

Provided, under separate cover, to the FDA New Jersey District Office is a field copy of the technical sections of this application, the application form, and the technical summary. Bayer certifies that the field copy is a true copy of the technical section contained in the archival and review copies of this submission.

The drug review process for this NDA is covered by the Prescription Drug User Fee Act (PDUFA II). Bayer certifies that the entire full application fee is being provided to FDA, under separate cover. The assigned User Fee number for this application is ID# 3626.

This application and all communications or materials submitted to the Agency in connection with this matter, now or in the future, constitute privileged and confidential commercial information and / or trade secrets that may not be disclosed to any third party without express prior written consent from Bayer.

We look forward to maintaining an open and collaborative dialogue to facilitate the overall review process. Please contact the undersigned at (973) 254-4673, or in my absence Ms. Karen Mancuso at (973) 254-4778 should you have any questions or requests.

Sincerely,
Bayer Corporation
Consumer Care Division

Rich Cuprys
Associate Director,
Regulatory Affairs

Submitted in duplicate
cc: Ms. Regina Brown
FDA New Jersey District Office