CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-076

CHEMISTRY REVIEW(S)

NOV 1 2 1999

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-076 **DATE REVIEWED:** 12-Nov-1999

REVIEW # 1 **REVIEWER:** Sue-Ching Lin

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	
Original	28-Jan-1999	29-Jan-1999	03-Feb-1999	
Amendments	05-Mar-1999			Draft labeling for containers (a response to FDA's 3/3/99 information request)
	15-Apr-1999			Amended patent certification
	15-Apr-1999			Six months stability data
	28-Apr-1999			Establishment addresses and CFNs (a response to FDA's information request)
	06-May-1999			4/28/99 Telecon minutes (CMC issues)
	28-May-1999			Electronic file of draft labeling
	02-Jun-1999			Response to CMC issues discussed in the 4/28/99 telephone conference
	13-Jul-1999			Revised analytical methods, validation (in accordance with the sponsor's 5/12/99 commitments issued during the pre-approval inspection at Syntex), 9 months stability data, and withdrawal of packaging equivalency protocol.
	26-Jul-1999			Addendum to environmental assessment
	12-Aug-1999			Proposed pouches for direct mail distribution and professional sampling
	16-Aug-1999			Response to FDA 483
	30-Sep-1999			Commit to submit supplement for changes to pseudoephedrine HCl
	04-Oct-1999			12 months stability data
	11-Oct-1999			Response to FDA's 9/21/99 CMC information request
	11-Oct-1999			Revised methods validation packages
	18-Oct-1999			Justification of Water Content Specification
	20-Oct-1999			Phase 4 CMC commitments
	12-Nov-1999			Sampling procedure for drug product

NAME & ADDRESS OF APPLICANT:

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

DRUG PRODUCT NAME

Proprietary: Aleve Cold and Sinus

Established: naproxen sodium and pseudoephedrine hydrochloride extended release tablets

Chem.Type/Ther.Class: 4S

PHARMACOL. CATEGORY: anti-inflammatory/analgesic/antipyretic/nasal decongestant

DOSAGE FORM: tablet

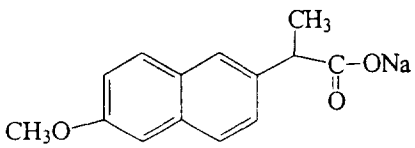
STRENGTHS: naproxen sodium 220 mg/ pseudoephedrine HCl 120 mg

ROUTE OF ADMINISTRATION: oral

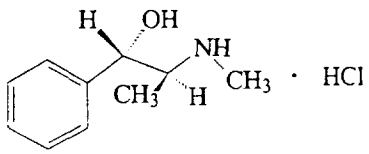
DISPENSED: ___Rx _X_ OTC

SPECIAL PRODUCTS: ___Yes _X_ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:



Naproxen Sodium $C_{14}H_{13}NaO_3$



$C_{10}H_{15}NO \cdot HCl$

Pseudoephedrine hydrochloride

SUPPORTING DOCUMENTS:

DMFs: See table below

DMF#	Type	Holder	Item/Component	Review Date	Status	LOA Date
	II	Syntex	naproxen sodium	10/8/99	Adequate*	10/29/98
	II			1/7/98	Adequate**	10/5/98
	III			7/24/98	Adequate	9/21/98
	III			10/14/99	Adequate*	5/22/98
	III			10/15/99	Adequate*	7/1/98

*DMFs reviewed by this reviewer for this NDA

**DMF for pseudoephedrine HCl was completely revised in the 6/24/99 amendment to reflect a change in synthesis process for ephedrine HCl, the penultimate intermediate. This amendment was reviewed by Kevin Swiss in HFD-570 and found to be deficient for the new process. However, the applicant had a telephone conference with Dr. Eric Sheinin, Director of Office of New Drug Chemistry on 8/9/99 and the FDA agreed that it is acceptable for Bayer to submit a supplement for the change to pseudoephedrine HCl synthesized by the new process, following approval of this NDA. Bayer commits to the continued use of pseudoephedrine HCl made by the current process and will not introduce into the marketplace drug product made with the new process pseudoephedrine HCl until approval of the supplement (see 9/30/99 amendment).

RELATED DOCUMENTS: NDA# 20-204 (Aleve®)

REMARKS:

2. The proprietary name "Aleve Cold and Sinus" has been found to be acceptable by the CDER Labeling and Nomenclature Committee (LNC) on 4/28/99. The LNC also recommends "naproxen sodium and pseudoephedrine hydrochloride extended release tablets" as the established name.

3. Drug substance: Detailed information on the drug substances is referenced to DMF for naproxen sodium and DMF for pseudoephedrine hydrochloride. DMF has been reviewed by this reviewer on 10/8/99 and found to be adequate. DMF was completely revised in the 6/24/99 amendment to reflect a change in synthesis process for ephedrine HCl, the penultimate intermediate. However, Bayer has committed to use pseudoephedrine HCl made by current process until a supplement is submitted to and approved by the FDA for the use of this drug substance made by the new process. DMF (excluding the 6/24/99 amendment) was reviewed on 1/7/98 and found to be adequate.

4. Drug product: This NDA has had many revisions in CMC section since the original submission. The following are two major changes:

   A list of CMC information request, which included deficiencies in compositions, specifications, manufacturing process, packaging, and stability protocol, was sent to the applicant by facsimile on 4/27/99 and the issues were discussed during the 4/28/99 telephone conference. Detailed information regarding the telecon can been found in the 5/6/99 amendment. Bayer responded to the information request in the 6/2/99 amendment.

   During the review process and the May 1999 pre-approval inspection at the drug product manufacturer, several deficiencies in manufacturing process and analytical methods were discovered. The firm satisfactorily responded to the FDA Form 483 in the 8/16/99 amendment and the Office of Compliance has issued an "acceptable recommendation for this site on 10/19/99. In response to this reviewer's comments during the inspection, a revised analytical method was developed and validated to assay degradation products. See attached reviewer's notes for details.

5. Phase 4 commitments: Bayer commits to submit the following information as a prior-approval supplement within one year of the product approval date:

   (a) Bayer will modify the product dissolution method and specifications to better reflect the product's *in vivo* performance.
   (b) Bayer will re-evaluate the Loss on Drying specification (%LOD) for the finished product using the new dissolution method (see above) and accumulated long term stability data.

6. Establishment evaluation was requested for each site used for manufacturing and control of the drug substance and drug product, as listed in section A-2 and B-3 of this review. The overall EES recommendation for this NDA is "acceptable". See attached establishment evaluation report.

7. Container/closure systems:
   a. 10-count carton: contains 1 blister card, with 10 tablets per blister card, 1 tablet per blister
   b. 20-count carton: contains 2 blister cards, with 10 tablets per blister card, 1 tablet per blister
   c. 1-count Pouch: will be used as individual sample

8. Environmental assessment: Information on environmental assessment was sent as a consult to Ms. Nancy Sager in HFD-357 for the review. The review has been completed and a FONSI (Finding of No Significant Impact) was recommended. Please see attached EA review.

9. Methods validation is pending. Methods validation packages were revised in response to the reviewer's comments and in accordance with the FDA guideline. The revised packages were submitted on 10/11/99. Copies of methods validation packages were sent to Philadelphia District Laboratory and San Juan District Laboratory on 10/19/99. Methods validation has not been completed by the laboratories but is not required for approval of the NDA.

10. Labeling: Labeling review will be completed by the OTC labeling reviewer. Please refer to the labeling review of this NDA.

CONCLUSIONS & RECOMMENDATIONS:

From the chemistry, manufacturing, and controls standpoint, this NDA may be approved. However, the letter to the applicant should include the phase 4 commitments as presented in item #5 above and the standard methods validation paragraph.

cc:
Orig. NDA 21-076
HFD-550/Division File
HFD-550/Mitra/Sue Lin
HFD-550/CSO/Schmidt
HFD-550/CFang/JHyde
HFD-550/ANoory/DBashaw
HFD-550/CChen
HFD-560/LHu
HFD-830/CChen

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