CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-076

PHARMACOLOGY REVIEW

1.1

Review and Evaluation of Pharmacology and Toxicology Data
HFD-550

JUL 23 1999

NDA: 21076 (Original Submission)
Sponsor: Bayer Corporation
Drug Name: Aleve Cold and Sinus Caplet (naproxen sodium (220mg) / pseudoephedrine hydrochloride (120mg)
Drug Class: NSAID / Nasal Decongestant for OTC Oral Use
Indication: Pain Reliever Fever Reducer / Nasal Decongestant
Dosage: One caplet every 12 hours
Submission Date: January 29, 1999
Review Completion Date: June 22, 1999
Reviewer: Conrad H. Chen, Ph.D
Related IND/NDA: [redacted] NDA 20204
Formulation:

COMPONENT	MG/TAB
Naproxen sodium	220.00
Pseudoephedrine hydrochloride, USP	120.00
Povidone, USP	[redacted]
Microcrystalline cellulose, NF	[redacted]
Lactose,	[redacted]
Hydroxypropyl methylcellulose	[redacted]
Hydroxypropyl methylcellulose	[redacted]
Talc, USP	[redacted]
Magnesium stearate, NF	[redacted]
Colloidal sillicon dioxide, NF	[redacted]
TOTAL	621.23

Introduction and Drug History: Aleve (naproxen sodium 220 mg, NDA 20204) is currently marketed as an OTC product. Pseudoephedrine 120 mg is also available as an OTC product in the market. The product of this NDA, Aleve Cold & Sinus OTC, is a bi-layer tablet containing the identical immediate-release formulation found in Aleve and the sustained-release matrix formula of pseudoephedrine hydrochloride found in a number of commercially available products.

During a pre-IND [redacted] meeting for this product on October 21, 1997, the sponsor was recommended by FDA to conduct the following preclinical studies for NDA.

1. A mutagenicity study- the Ames test.
2. A teratogenicity study (Segment II) in one animal species. It was suggested to the sponsor that published literature might also be acceptable in lieu of the test.

In the NDA submission, the sponsor presented the above studies for review and referred to IND [redacted] for other information.

The combination of naproxen sodium and pseudoephedrine hydrochloride [redacted] has been available in Mexico as a prescription drug since July 1993. This combination product is not available in any other country for prescription or OTC use.

Preclinical Study:

1. **Bacterial Reverse Mutation Assay:** (Vol. 7, p.236)
   The study was conducted from May 15 to August 17, 1998 by [redacted] in compliance with the US FDA Good Laboratory Practice Regulations. The study was conducted using a combination of naproxen sodium – pseudoephedrine hydrochloride in a 2.2 to 1.2 ratio. The tester strains used were the [redacted] induced rat liver S9 was used as the metabolic activation system. The maximum concentration used in the assay was 5000 µg per plate. No precipitate or appreciable toxicity occurred in the assay.

   The results of this test showed that, under the conditions of assay, this product did not cause a positive response with any of the tester strains in the presence and absence of rat liver S9. The summary of the results is presented in the following two tables.

Salmonella Mutagenicity Assay, Summary of Results

Test Article Id : Naproxen sodium - pseudoephedrine hydrochlorine combination in a 2.2 to 1.2 ratio
Study Number : G98AV24-25.502 Experiment No : B1

Average Revertants Per Plate ± Standard Deviation

Liver Microsomes: None

Dose (µg)	TA98	TA100	TA1535	TA1537
0.0	17 ± 3	132 ± 7	7 ± 3	6 ± 3
100	17 ± 2	121 ± 19	12 ± 3	6 ± 3
333	16 ± 5	111 ± 15	10 ± 1	3 ± 1
1000	16 ± 2	98 ± 6	10 ± 2	5 ± 3
3333	12 ± 2	67 ± 10	7 ± 4	3 ± 1
5000	14 ± 4	80 ± 8	8 ± 1	6 ± 2
Pos	342 ± 26	511 ± 32	424 ± 45	853 ± 224

Liver Microsomes: Rat liver S9

Dose (µg)	TA98	TA100	TA1535	TA1537
0.0	19 ± 3	131 ± 6	11 ± 2	7 ± 1
100	20 ± 3	118 ± 23	12 ± 2	10 ± 4
333	15 ± 5	113 ± 5	11 ± 2	5 ± 3
1000	18 ± 3	99 ± 5	13 ± 6	8 ± 3
3333	13 ± 3	87 ± 7	10 ± 5	3 ± 2
5000	18 ± 6	95 ± 32	9 ± 1	6 ± 3
Pos	792 ± 28	872 ± 323	94 ± 37	120 ± 43

0.0 = Vehicle plating aliquot of 50 µL
Pos = Positive Control concentrations as specified in Materials and Methods section.

E. coli Mutagenicity Assay, Summary of Results

Test Article Id : Naproxen sodium - pseudoephedrine hydrochlorine combination in a 2.2 to 1.2 ratio
Study Number : G98AV24-25.502 Experiment No : B2

Average Revertants Per Plate ± Standard Deviation

Liver Microsomes: None

Dose (µg)	WP2 uvrA
0.0	17 ± 2
100	12 ± 2
333	14 ± 2
1000	14 ± 1
3333	18 ± 2
5000	14 ± 1
Pos	184 ± 18

Liver Microsomes: Rat liver S9

Dose (µg)	WP2 uvrA
0.0	18 ± 2
100	15 ± 1
333	14 ± 2
1000	17 ± 6
3333	11 ± 2
5000	12 ± 5
Pos	84 ± 17

0.0 = Vehicle plating aliquot of 50 µL
Pos = Positive Control concentrations as specified in Materials and Methods section.

2. **Reproduction (Segment II) Study in Rats:** (Vol. 7, p.4)
The study was conducted by [redacted] from May 25, 1998 to January 5, 1999, in compliance with US FDA GLP Regulations. Twenty-five pregnant Sprague-Dawley rats were assigned to each of the six dosage groups. Dosages were administered at a dosage volume of 10 ml/kg by intubation from Days 7 to 17 of gestation.

Dosage Group	Naproxen Sodium (mg/kg/day)	Pseudoephedrine Hydrochloride (mg/kg/day)
I	0 (vehicle)	0 (vehicle)
II	8.8	4.8
III	17.6	9.6
IV	35.2	19.2
V	35.2	0
VI	0	19.2

All rats were sacrificed by carbon monoxide asphyxiation on Day 20 of gestation. Approximately one-half of the fetuses in each litter were examined for soft tissue alterations and the remaining fetuses in each litter were examined for skeletal alterations.
Six rats administered the highest dosage of naproxen sodium alone (Group V) and five rats administered the highest dosage of naproxen sodium in combination with pseudoephedrine hydrochloride (Group IV) died or were sacrificed in moribund condition. Most of these animals had adhesions of the viscera and fluid in the abdominal cavity upon necropsy. These were probably caused by GI ulceration induced by NSAID. Many of these animals also had enlarged adrenal glands and enlarged spleen.

No clinical observations related to test article were seen for rats in Groups I, II, III, or VI. The animals in Groups IV and V showed dehydration, emaciation, chromorhinorrhea, urine-

stained abdominal fur, pale appearance and /or pale eyes, cold to touch and soft or liquid feces. Red perivaginal, perioral or perianal substance was considered to be related to test article administration.

Body weight gains and feed consumption for the entire gestation period (gestation days 0 to 20) were significantly reduced in Groups IV and V. The reductions in maternal body weight gains were 57.7 % for Gp IV and 61 % for Gp V, respectively. The reductions in feed consumption were 22.3 % for Gp IV and 20.6 % for Gp V, respectively. These parameters were also reduced in other treated groups on certain gestation days but no clear dose-response trend was observed. It was found that the dosages as high as 35.2 mg/kg/day of naproxen sodium, either alone or in combination with 19.2 mg/kg/day pseudoephedrine hydrochloride (Groups V and IV), did not affect several parameters evaluated at Cesarean-sectioning. These parameters included litter averages for corpora lutea, implantations, litter sizes, live and dead fetuses, early and late resorptions and percent live male fetuses. (The apparent reductions in mean number of corpora lutea, implantations, litter sizes and live fetuses in Group IV, which amount to less than 10 % in each, are eliminated when values for four litters of ten or fewer conceptuses are excluded from statistical summarization).

Fetal body weights paralleled body weight findings for the dams. While fetal body weights were normal in Groups I, II, III and VI; they were significantly reduced in Groups IV (approximately 10 %) and V (approximately 17 %). In Groups I and II, no increase in incidence of fetal variations was seen. Fetal variations, mainly delayed ossifications, occurred in Groups III, IV and V. Those variations included: (1) significant delays in pelvic ossification in Groups III and V and (2) significant reduction in the number of ossified caudal vertebrae, manubrium, sternal centers, xyphoid, metacarpals and metatarsals in Groups IV and V. The incidence of cervical ribs was significantly increased in Groups III and IV. All fetal gross external, soft tissue and all other skeletal alterations were considered unrelated to drug administrations because incidences were not dosage-dependent and were within the ranges of historical controls. All fetal alterations that occurred in this study are described in the following tables:

FETAL SOFT TISSUE ALTERATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V	VI
DOSAGE (MG/KG/DAY)[a]		0/0	8.8/4.8	17.6/9.6	35.2/19.2	35.2/0	0/19.2
LITTERS EVALUATED	N	25	24	25	17	18[b]	24
FETUSES EVALUATED	N	164	177	168	102	133	172
LIVE	N	164	177	168	102	126	172
DEAD	N	0	0	0	0	-[b]	0
VESSELS: UMBILICAL ARTERY DESCENDED TO THE LEFT OF THE URINARY BLADDER							
LITTER INCIDENCE	N(%)	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	1 (4.2)
FETAL INCIDENCE	N(%)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.6)
EYES: MICROPHTHALMIA							
LITTER INCIDENCE	N(%)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
FETAL INCIDENCE	N(%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
KIDNEYS: SMALL							
LITTER INCIDENCE	N(%)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
FETAL INCIDENCE	N(%)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

a. Dosage occurred on days 7 through 17 of gestation.
b. Dead fetuses were excluded from group averages and statistical analyses.

FETAL SKELETAL ALTERATIONS - SUMMARY (PAGE 1)
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV	V	VI
DOSAGE (MG/KG/DAY)a		0/0	8.8/4.8	17.6/9.6	35.2/19.2	35.2/0	0/19.2
LITTERS EVALUATED	N	25	24	25	17	18b	24
FETUSES EVALUATED	N	178	191	182	108	143	183
LIVE	N	178	191	182	108	136	183
DEAD	N	0	0	0	0	7b	0
SKULL: SPHENOID, INCOMPLETELY OSSIFIED							
LITTER INCIDENCE	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0-0)
FETAL INCIDENCE	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)m	0 (0-0)
CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA							
LITTER INCIDENCE	N(%)	0 (0.0)	0 (0.0)	3 (12.0)**	3 (17.6)**	1 (5.3)	0 (0.0)
FETAL INCIDENCE	N(%)	0 (0.0)	0 (0.0)	3 (1.6)**	3 (2.8)**	1 (0.7)	0 (0.0)
THORACIC VERTEBRAE: CENTRUM, BIFID							
LITTER INCIDENCE	N (%)	2 (8.0)	1 (4.2)	5 (20.0)	0 (0.0)	1 (5.3)	4 (16.7)
FETAL INCIDENCE	N (%)	3 (1.7)	1 (0.5)	6 (3.3)	0 (0.0)	1 (0.7)	4 (2.2)
LUMBAR VERTEBRAE: ARCH, INCOMPLETELY OSSIFIED							
LITTER INCIDENCE	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)
FETAL INCIDENCE	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)m	0 (0.0)
RIBS: INCOMPLETELY OSSIFIED (HYPOPLASTIC)							
LITTER INCIDENCE	N (%)	1 (4.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
FETAL INCIDENCE	N (%)	1 (0.6)c	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
STERNAL CENTRA SUMMARIZATION (Includes incompletely ossified and not ossified sternal centra):							
LITTER INCIDENCE	N (%)	2 (8.0)	3 (12.5)	2 (8.0)	1(5.9)	2 (11.1)	2 (8.3)
FETAL INCIDENCE	N (%)	2 (1.1)d	7(3.7)e,f	2 (1.1)g,h	1(0.9)	4 (2.9)i,k,l	4 (2.2)
STERNAL CENTRA: IST, NOT OSSIFIED							
LITTER INCIDENCE	N (%)	0 (0.0)	1 (4.2)	1 (4.0)	1(5.9)	2 (10.5)	1 (4.2)
FETAL INCIDENCE	N (%)	0 (0.0)	1 (0-5)	1 (0.5)h	1(0.9)	2 (1.5)i,l	1 (0.5)
STERNAL CENTRA: IST, INCOMPLETELY OSSIFIED							
LITTER INCIDENCE	N (%)	2 (8.0)	3 (12.5)	1 (4.0)	0 (0)	1 (5.3)	2 (8.3)
FETAL INCIDENCE	N (%)	2 (1.1)d	6 (3.1)e,f	1 (0.5)g	0 (0.0)	2 (1.5)k	3 (1.6)

FETAL SKELETAL ALTERATIONS – SUMMARY (PAGE 2)

DOSAGE GROUP		I	II	III	IV	V	VI
DOSAGE(MG/KG/DAY)a		0/0	8. 8/4.8	17.6/9.6	35.2/19.2	35.2/0	0/19.2
LITTERS EVALUATED	N	25	24	25	17	18b	24
FETUSES EVALUATED	N	178	191	182	108	143	183
LIVE	N	178	191	182	108	136	183
DEAD	N	0	0	0	0	7b	0
STERNAL CENTRA: 2ND, INCOMPLETELY OSSIFIED							
LITTER INCIDENCE	N (%)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
FETAL INCIDENCE	N (%)	0 (0.0)	1 (0.5)f	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PELVIS: SUMMARIZATION (Includes incompletely ossified and not ossified pubes and ischia):							
LITTER INCIDENCE	N (%)	3 (12.0)	3 (12.5)	5 (20.0)	0 (0.0)	3 (17.7)	0 (0.0)
FETAL INCIDENCE	N (%)	4 (2.2)c,d	4 (2.1)e	14 (7.7)**g, h	0 (0.0)	8 (5.9)**i-m	0 (0.0)
PELVIS: PUBIS, NOT OSSIFIED							
LITTER INCIDENCE	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)**	0 (0.0)
FETAL INCIDENCE	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)**i	0 (0.0)
PELVIS: ISCHIUM, INCOMPLETELY OSSIFIED							
LITTER INCIDENCE	N (%)	1 (4.0)	0 (0.0)	1 (4.0)	0 (0.0)	2 (10.5)	0 (0.0)
FETAL INCIDENCE	N (%)	1 (0.6)c	0 (0.0)	3 (1.6)	0 (0.0)	3 (2.2)j, l, m	0 (0.0)
PELVIS: PUBIS, INCOMPLETELY OSSIFIED							
LITTER INCIDENCE	N (%)	3 (12.0)	3 (12.5)	4 (16.0)	0 (0.0)	2 (10.5)	0 (0.0)
FETAL INCIDENCE	N (%)	3 (1.7)c, d	4 (2.1)e	11 (6.0)**g, h	0 (0.0)	6 (4.4)*j-m	0 (0.0)

a. Dosage Occurred on days 7 through 17 of gestation; b. Dead fetuses were excluded from group averages and statistical analyses; c. Fetus 8309-3 had other skeletal alterations; d. Fetus 8321-1 had other skeletal alterations; e. Fetus 8344-17 had other skeletal alterations; f. Fetus 8349-13 had other skeletal alterations; g. Fetus 8369-8 had other skeletal alterations; h. Fetus 8375-1 had other skeletal alterations; i. Fetus 8414-9 had other skeletal alterations; J. Fetus 6414-12 had other skeletal alterations; k. Fetus 8419-1 had other skeletal alterations; l. Fetus 8419-13 had other skeletal alterations; m. Fetus 8419-15 had other skeletal alterations; * Significantly different from the vehicle control group value ($p \leq 0.05$); ** Significantly different from the vehicle control group value ($p < 0.01$).

FETAL OSSIFICATION SITES - CAESAREAN-DELIVERED LIVE FETUSES (DAY 20 OF GESTATION) – SUMMARY

DOSAGE GROUP		I	II	III	IV	V	VI
DOSAGE (MG/KG/DAY)a		0/0	8.8/4.8	17.6/9.6	35.2/19.2	35.2/0	0/19.2
LITTERS EXAMINED	N	25	24	25	17	18	24
FETUSES EXAMINED	N	178	191	182	108	136	183
HYOID	MEAN±S.D.	0.94 ± 0.10	0.83 ± 0.24	0.94 ± 0.11	0.94 ± 0. 3	0.96 ± 0.09	0.90 ± 0.13
VERTEBRAE							
CERVICAL	MEAN±S.D.	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00
THORACIC	MEAN±S.D.	13.06 ± 0.13	13.06 ± 0.16	13.06 ± 0.17	13.06 ± 0.15	13.01± 0.03	13.03 ± 0.07
LUMBAR	MEAN±S.D.	5.94 ± 0.13	5.93 ± 0.16	5.94 ± 0.17	5.94 ± 0.15	5.99 ± 0.03	5.97 ± 0.08
SACRAL	MEAN±S.D.	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	2.99 ± 0.05	3.00 ± 0.00
CAUDAL	MEAN±S.D.	4.86 ± 0.52	4.71 ± 0.40	4.81 ± 0.56	4.52 ± 0.58	4.18 ± 0.68**	4.72 ± 0.52
RIBS (PAIRS)	MEAN±S.D.	13.04 ± 0.09	13.04 ± 0.11	13.04 ± 0.10	13.05 ± 0.14	13.01 ± 0.03	13.02 ± 0.04
STERNUM							
MANUBRIUM	MEAN±S.D.	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	0.98 ± 0.06**	1.00 ± 0.000
STERNAL CENTERS	MEAN±S.D.	3.80 ± 0.22	3.65 ± 0.28	3.74 ± 0.29	3.37 ± 0.35**	3.50 ± 0.53	3.70 ± 0.29
XIPHOID	MEAN±S.D.	1.00 ± 0.00	1.00 ± 0.02	1.00 ± 0.02	0.98 ± 0.07	0.89 ± 0.25**	1.00 ± 0.00
FORELIMB b							
CARPALS	MEAN±S D.	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
METACARPALS	MEAN+S.D.	3.76 ± 0.26	3.56 ± 0.31	3.67 ± 0.32	3.50 ± 0.41*	3.33 ± 0.35**	3.66 ± 0.27
DIGITS	MEAN±S.D.	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00
PHALANGES	MEAN±S.D.	5.12 ± 0.24	5.00 ± 0.00	5.07 ± 0.21	5.05 ± 0.12	4.98 ± 0.17	5.11 ± 0.29
HINDLIMB b							
TARSALS	MEAN±S.D.	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
METATARSALS	MEAN±S.D.	3.99 ± 0.04	4.00 ± 0.00	4.00 ± 0.02	3.98 ± 0.05	3.93 ± 0.17*	4.00 ± 0.00
DIGITS	MEAN±S.D.	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00
PHALANGES	MEAN±S.D.	5.00 ± 0.00	5.00 ± 0.00	4.98 ± 0.12	4.87 ± 0.38	4.96 ± 0.16	5.00 ± 0.00

a. Dosage occurred on days 7 through 17 of gestation.
b. Calculated as average per limb.
* Significantly different from the vehicle control group value ($p<0.05$).
** Significantly different from the vehicle control group value ($p<0.01$).

Overall Summary:

Aleve (naproxen sodium 220 mg, NDA 20204) is currently marketed as an OTC product. Pseudoephedrine 120 mg is also available as an OTC product in the market. The product of this NDA, Aleve Cold & Sinus OTC, is a bi-layer tablet containing the identical immediate-release formulation found in Aleve and the sustained-release matrix formula of pseudoephedrine hydrochloride found in a number of commercially available products. This combination drug product is intended for OTC use as a pain reliever / fever reducer / nasal decongestant. The combination of naproxen sodium and pseudoephedrine hydrochloride has been available in Mexico as a prescription drug since July 1993. This combination product is not available in any other country for prescription or OTC use.

In this NDA, the applicant has submitted a bacterial reverse mutation test (Ames test) and a teratogenicity study in rats as recommended by the FDA during a pre-meeting for (NDA 21076) on October 21, 1997. The results from the mutagenicity study showed that the combination drug products (naproxen sodium : pseudoephedrine hydrochloride in a 2.2 to 1.2 ratio) were not mutagenic in the bacterial systems.

The teratogenicity study showed that at the maternally toxic dose of 35.2 mg kg/day naproxen sodium (with or without 19.2 mg/kg/day pseudoephedrine hydrochloride) reduced fetal weights and several delayed skeletal ossifications occurred. However, no potentiation of the fetal effects of naproxen sodium by pseudoephedrine hydrochloride was found. Some findings in delayed ossification were not dosage-dependent or were within the historical ranges.

No other fetal effects except the increased incidence of cervical ribs (at 17.6 9.6 and 35.2/19.2 combinations) were observed. The litter incidences and fetal incidences of cervical ribs were 12.0 % and 1.6 % for Group III and 17.6 % and 2.8 % for Group IV, respectively. However, the cervical ribs had a high historical incidence (litter: range 0-20 %, average 3.78 %; fetal: range 0-2.7 %, average 0.51 %). The observed maternal toxic effects included death, clinical observations (reductions in body weight, body weight gain and feed consumption values) and necropsy observations (e.g. adhesions of the viscera and fluid in abdominal cavity). The maternal NOAEL is considered as 17.6/9.6 mg/kg/day of naproxen sodium / pseudoephedrine hydrochloride in this study.

The labeling of the currently marketed Anaprox [redacted] stated that there was no evidence of impaired fertility or harm to the fetus at 20 mg/kg/day of naproxen sodium in rats. In the current NDA, reduced fetal weights and delayed skeletal ossification were reported at 35.2 mg/kg/day of naproxen sodium and 19.2 mg/kg/day of pseudoephedrine hydrochloride in rat teratogenicity study. However, this dosage level was considered as a maternally toxic dose in the study. No potentiation of fetal effects of naproxen sodium by pseudoephedrine hydrochloride was found.

Recommendation:

The pharmacology reviewer recommends the approval of NDA 21076, Aleve Cold & Sinus for OTC.

/S/

Conrad H. Chen, Ph.D.
Reviewing Pharmacologist

/S/

7-23-99

cc:
NDA 21076/Div.File
NDA 21076/Original NDA
HFD-550/MO/Fang
HFD-550/Pharm/Chenco
HFD-550/TLPharm/Weir
HFD-550/Chem/Lin
HFD-550/CSO/Schmidt
HFD-345