CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

17-581 / S-004

Trade Name: Naprosyn

Generic Name: (naproxen)

Sponsor: Syntex Inc.

Approval Date: July 15, 1980

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-581 / S-004

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Statistical Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-581 / S-004

APPROVAL LETTER

NDA 17-581/S-001/S-004

JUL 15 1980

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

JUL 15 1980

Syntex Corporation
Attention:
3401 Hillview Avenue
Palo Alto, California 94304

Gentlemen:

Please refer to your resubmitted supplemental new drug applications dated September 21, 1979 (S-001), and February 20, 1979 (S-004), submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Naprosyn Tablets (naproxen).

We also refer to your submission of June 2, 1980, containing final printed labeling and to your amendments for S-004 dated April 13, and October 25, 1979, March 21 and 31, and April 11, 1980.

Supplement S-001 provides for the additional indication of osteoarthritis. Supplement S-004 provides for a 375 mg tablet.

We have completed the review of these supplemental applications as amended and they are approved. However, at the next printing under "Precautions" there should be a "Pediatric Use" section and in the first sentence under "Dosage and Administration" the words "in adults" should be added after "dose."

Our letter of March 11, 1976 detailed the conditions relating to the approval of this application.

Sincerely yours,

H.F.

Marion J. Finkel, M.D.
Associate Director
for New Drug Evaluation
Bureau of Drugs

cc: LOS-DO
Orig. NDA
HFD-100
HFD-180
HFD-150
HFD-150/Doc. Rm.
HFD-160/EMcGoodwin/6/19/80/ts/6/23/80
Revised/rh for/ds/7/11/80
R/D init. by: JBHarter/6/19/80
Ochote/6/25/80
EMcGoodwin/6/25/80
MMHein/6/26/80
RPatel/6/26/80
RHWood/6/26/80
JCrotty for JHarter
RDerussi/6/26/80
WJGyarfas/6/26/80

APPROVED
1240

MABateman 7/14/80

7-14-80

7/14/80

7/14/80

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-581 / S-004

APPROVABLE LETTER(S)

JAN 21 1979

NDA 17-581/S-004

Syntex Laboratories Inc.
Attention: James D. Mutch
Director Regulatory Affairs
3401 Hillview Avenue
Palo Alto, California 94304

Gentlemen:

We acknowledge the receipt on October 2, October 27, and November 24, 1978 of your communications dated September 28, October 25, and November 20, 1978 regarding your supplemental new drug application of May 5, 1977 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Naprosyn (naproxen) Tablets.

The supplemental application provides for the marketing of a 375 mg NAPROSYN tablet.

We have completed our review of this supplemental application. However, before we are able to reach a final conclusion the following additional information is necessary:

1. The specifications for the [redacted] should include:

   a. weight variation

   b. content uniformity

   c. [redacted]

2. It is suggested that the specific rotation for the [redacted] be revised to correspond to a [redacted] naproxen content. The specification for the naproxen content should also be [redacted]

3. The dissolution data suggests that the dissolution limit for the [redacted] should be [redacted] from [redacted] in 30 minutes to [redacted] in 30 minutes. A paragraph describing the dissolution specifications should be included. Mean values should not be

used in the calculations. See USP XIX and its 4th supplement.

Please submit the above information promptly.

Sincerely yours,

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

cc: LOS-DO
Orig. NDA
HFD-150 AWCoulter 17 Jan 78
HFD-150/AWCoulter/12/21/78/ls/1/11/79/1/17/79
R/D init. by: RHWood/1/5/79

REVIEWED/WAITING FIRM RHwood 1/17/79

WJGyarfas 1/18/79

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-581 / S-004

APPROVED LABELING

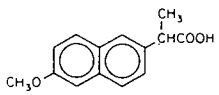
NAPROSYN®
(naproxen)

Tablets

DESCRIPTION

NAPROSYN® (naproxen) tablets for oral administration each contain 250 mg or 375 mg of naproxen. NAPROSYN is a non-steroidal anti-inflammatory agent with analgesic and antipyretic properties and is related to the arylacetic acid class of drugs.

The chemical name for naproxen is (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid. It has the following structure:



naproxen

Naproxen is an odorless, white to off-white crystalline substance. It is lipid soluble, practically insoluble in water at low pH and freely soluble in water at high pH.

CLINICAL PHARMACOLOGY

Naproxen is rapidly and completely absorbed from the gastrointestinal tract. After administration of naproxen, peak plasma levels of naproxen anion are attained in 2 to 4 hours, with steady-state conditions normally achieved after 4-5 doses. The mean biological half-life of the anion in humans is approximately 13 hours, and at therapeutic levels it is greater than 99% albumin bound. Approximately 95% of the dose is excreted in the urine, primarily as naproxen, 6-0-desmethyl naproxen or their conjugates. The rate of excretion has been found to coincide closely with the rate of drug disappearance from the plasma. The drug does not induce metabolizing enzymes. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.

The drug was studied in patients with rheumatoid arthritis and osteoarthritis. It is not a corticosteroid. Improvement in patients treated for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, a reduction in pain, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time.

In patients with osteoarthritis, the therapeutic action of the drug has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

In clinical studies in patients with rheumatoid arthritis and osteoarthritis, the drug has been shown to be comparable to aspirin in controlling the aforementioned measures of disease activity, but the frequency and severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less than in the aspirin-treated patients. It is not known whether the drug causes less peptic ulceration than aspirin.

The drug may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether the drug could be used in conjunction with partially effective doses of corticosteroid for a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts the drug did result in greater improvement. Its use in combination with salicylates is not recommended because data are inadequate to demonstrate that the drug produces greater improvement over that achieved with aspirin alone. Further, there is some evidence that aspirin increases the rate of excretion of the drug.

Generally, improvement due to the drug has not been found to be dependent on age, sex, severity or duration of disease.

In ^{51}Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg of the drug has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

INDICATIONS AND USAGE

NAPROSYN (naproxen) is indicated for the treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

The safety and effectiveness of the drug in children have not been established.

CONTRAINDICATIONS

Naproxen is contraindicated in patients who have shown hypersensitivity to it. Because the potential exists for cross-sensitivity reactions, the drug should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory drugs induce the syndrome of asthma, rhinitis, or urticaria.

WARNINGS

Gastrointestinal bleeding, sometimes severe, and occasionally fatal, has been reported in patients receiving the drug. Among 960 patients treated for rheumatoid arthritis or osteoarthritis during the course of clinical trials in the United States (260 treated for more than two years), 16 cases of peptic ulceration were reported. More than half were on concomitant corticosteroid and/or salicylate therapy and about a third had a prior history of peptic ulcer. Gastrointestinal bleeding, including nine potentially serious cases, was also reported in this population. These were not always preceded by premonitory gastrointestinal symptoms. Although most of the patients with serious bleeding were receiving concomitant therapy and had a history of peptic ulcer disease, it should be kept in mind that the drug also has the potential for causing gastrointestinal bleeding on its own. Therefore, it should be administered to patients with active gastric and duodenal ulcers only under close supervision.

PRECAUTIONS

General:

Because of adverse eye findings in animal studies with drugs of this class it is recommended that ophthalmic studies be carried out within a reasonable period of time after starting therapy and at periodic intervals thereafter if the drug is to be used for an extended period of time.

In chronic studies in laboratory animals, the drug has caused nephritis. Glomerular nephritis, interstitial nephritis and nephrotic syndrome have been reported. Since the drug is eliminated to a large extent from the body by urinary excretion via glomerular filtration, this drug should be used with great caution in patients with significantly impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. In clinical trials a few patients developed mild elevations in BUN accompanied by no other signs or symptoms.

If steroid dosage is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Patients with initial hemoglobin values of 10 grams or less who are to receive long-term therapy should have hemoglobin values determined frequently.

Peripheral edema has been observed in some patients. It is possible that patients with questionable or compromised car-

naproxen

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Patients with initial hemoglobin values of 10 grams or less who are to receive long-term therapy should have hemoglobin values determined frequently.

Peripheral edema has been observed in some patients. It is possible that patients with questionable or compromised cardiac function may be at a greater risk when taking the drug.

Information for Patients:

Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with the drug.

Drug Interactions:

In vitro studies have shown that naproxen anion, because of its affinity for protein, may displace from their binding sites other drugs which are also albumin-bound. Theoretically, the naproxen anion itself could likewise be displaced. Short-term controlled studies failed to show that taking the drug significantly affects prothrombin times when administered to individuals on coumarin-type anticoagulants. Caution is advised nonetheless, since interactions have been seen with other non-steroidal agents of this class. Similarly, patients receiving the drug and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Drug/Laboratory Test Interactions:

The drug may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of the drug may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with the drug be temporarily discontinued 72 hours before adrenal function tests are performed.

The drug may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

Carcinogenesis:

A two-year study was performed in rats to evaluate the carcinogenic potential of the drug. No evidence of carcinogenicity was found.

Pregnancy:

Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats, rabbits and mice at doses up to six times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to the drug. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, the drug should not be used during pregnancy unless clearly needed.

Non-teratogenic Effects: In rats, pregnancy was prolonged when the drug was given before the onset of labor; where it was given after the delivery process had begun, labor was protracted.

Nursing Mothers:

Caution should be exercised if the drug is administered to a nursing woman since the naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma.

ADVERSE REACTIONS

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below.

Incidence greater than 1%

Gastrointestinal: The most frequent complaints reported related to the gastrointestinal tract. They were: constipation*, heartburn*, abdominal pain*, nausea*, dyspepsia, diarrhea, stomatitis.

Central Nervous System: Headache*, dizziness*, drowsiness*, lightheadedness, vertigo.

Dermatologic: Itching (pruritis)*, skin eruptions*, ecchymoses*, sweating, purpura.

Special Senses: Tinnitus*, hearing disturbances, visual disturbances.

Cardiovascular: Edema*, dyspnea*, palpitations.

General: Thirst.

*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

Incidence less than 1%

Probable Causal Relationship:

The following adverse reactions were reported less frequently than 1% during controlled clinical trials and through voluntary reports since marketing. The probability of a causal relationship exists between the drug and these adverse reactions:

- congestive heart failure
- renal disease
- glomerular nephritis
- interstitial nephritis
- nephrotic syndrome
- abnormal liver function tests
- hematuria
- jaundice
- thrombocytopenia
- leukopenia
- granulocytopenia
- gastrointestinal bleeding
- peptic ulceration with bleeding and/or perforation
- hematemesis
- melana
- vomiting
- eosinophilia
- pyrexia (chills and fever)
- skin rashes
- menstrual disorders
- myalgia and muscle weakness
- alopecia
- inability to concentrate
- depression
- malaise
- dream abnormalities

Causal Relationship Unknown:

Other reactions have been reported in circumstances in which a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore these observations are being listed to serve as alerting information to the physicians:

- angioneurotic edema
- agranulocytosis
- aplastic anemia
- hemolytic anemia
- hypoglycemia
- hyperglycemia
- urticaria

OVERDOSAGE

Significant overdosage may be characterized by drowsiness, heartburn, indigestion, nausea or vomiting. No evidence of toxicity or late sequelae have been reported 5 to 15 months after ingestion for three to seven days of doses up to 3,000 mg of naproxen. One patient ingested a single dose of 25 g of naproxen and experienced mild nausea and indigestion. It is not known what dose of the drug would be life threatening. The oral LD_{50} of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters and greater than 1000 mg/kg in dogs.

Should a patient ingest a large number of tablets, accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. Animal studies suggest that the prompt administration of 5 grams of activated charcoal would tend to reduce markedly the absorption of the drug. It is not known if the drug is dialyzable.

DOSAGE AND ADMINISTRATION

The recommended starting dose is one 250 mg tablet or one 375 mg tablet twice daily (morning and evening). During long-term administration, the dose may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. Daily doses higher than 1000 mg have not been studied. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary. Symptomatic improvement in arthritis usually begins within two weeks. However, if improvement is not seen within this period, a trial for an additional two weeks should be considered.

HOW SUPPLIED

NAPROSYN (naproxen) is available in scored tablets of 250 mg (yellow) in bottles of 100 tablets (NDC 18393-272-42) and 500 tablets (NDC 18393-272-62) or in cartons of 100 individually blister packed tablets (NDC 18393-272-53) and in 375 mg (peach) tablets in bottles of 100 tablets (NDC 18393-273-42) and 500 tablets (NDC 18393-273-62). Store at room temperature in well-closed containers; dispense in light-resistant containers.

U.S. Patent No. 3,904,682 and others.

the form of floating tablets at a concentration of approximately 1/5 of that found in the plasma.

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Incidence greater than 1%

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General: Thirst.

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congestive heart failure
renal disease
glomerular nephritis
interstitial nephritis
nephrotic syndrome
abnormal liver function tests
hematuria
jaundice
thrombocytopenia
leukopenia
granulocytopenia
gastrointestinal bleeding
peptic ulceration with bleeding and/or perforation
hematemesis
melena
vomiting
eosinophilia
pyrexia (chills and fever)
skin rashes
menstrual disorders
myalgia and muscle weakness
alopecia
inability to concentrate
depression
malaise
dream abnormalities

Causal Relationship Unknown:

Other reactions have been reported in circumstances in which a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore these observations are being listed to serve as alerting information to the physicians:

angioneurotic edema
agranulocytosis
aplastic anemia
hemolytic anemia
hypoglycemia
hyperglycemia
urticaria

OVERDOSAGE

Significant overdosage may be characterized by drowsiness, heartburn, indigestion, nausea or vomiting. No evidence of toxicity or late sequelae have been reported 5 to 15 months after ingestion for three to seven days of doses up to 3,000 mg of naproxen. One patient ingested a single dose of 25 g of naproxen and experienced mild nausea and indigestion. It is not known what dose of the drug would be life threatening. The oral LD_{50} of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters and greater than 1000 mg/kg in dogs.

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U.S. Patent No. 3,904,682 and others.

SYNTEX PUERTO RICO, INC.
Humacao, P.R., 00661

02-272-42-14

May 1980

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-581 / S-004

CHEMISTRY REVIEW(S)

JAN 21 1979

DIVISION OF ONCOLOGY AND RADIOPHARMACEUTICAL DRUG PRODUCTS

CHEMIST'S REVIEW

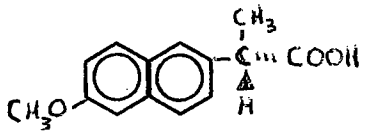
A. 1. NDA: 17-581/S-004 Date Completed 7/31/78
Sponsor: Syntex Croporation
Address: Palo Alto, California 94304

2. Product Name(s):
Proprietary: NAPROSYN^{R}
Non-proprietary: Naproxen
USAN: Naproxen
Code Name and/or Number: RS-3540

3. Dosage Form(s) and Route(s) of Administration:
Rx Tablet 250mg : — tablet

4. Pharmacological Category:
Anti-inflammatory

5. Structural Formula and Chemical Name:



(+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid

B. 1. Initial Submission:
Supplement submitted May 5, 1977. Received HFD-150 5/9/77.

2. Amendments: None

3. Supporting IND, NDA, MF, and Letter of Authorization:

4. Related Documents (IND's, NDA's, etc.): None

C. Remarks:
This supplement provides data to permit the marketing of a 375mg NAPROSYN^{R} tablet. The enclosed information contains:

a. A clinical study reporting bioequivalence of the proposed 375mg tablet with the approved 125mg tablet.

b. Manufactuirng and control information for the 375 mg tablet.

c. Labels and labeling

The July 1, 1977 submission corrects a typographical error appearing on page 1 of EIAR, page 4 (summary), and page 46 (quantitative composition).

The same methodology is used for testing the 375mg tablet that is used for the 125mg and 250mg tablets.

D. Conclusions and/or Recommendations:

Request submission of market package when available.

Stability data supports ——— expiration date.

Have Biopharmaceutics (HFD-520) check bioavailability data in this supplement. Sent to Dr. Cabana HFD-520. Dated 8/21/78.

Methods validation initiated on 23 Aug. 78.

A. W. Coulter

A. W. Coulter, Ph.D.

cc:
ORIG. NDA 17-581/S-004
HFD-102/Dr.Kumkumian
HFD-150
HFD-150/AWCoulter/7/31/78
R/D Endorsed: RHWood/8/3/78
mk/T/F: 8/29/78

RHWood 1/5/79

1/5/79

WITHHOLD 9 PAGE(S)

B4

Chemistry Review 1

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: FDA/BD/NDE/DORDP

2. NDA NUMBER: 17-581

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Syntex Corporation
Palo Alto, CA 94304

4. AF NUMBER

JUL 9 - 1979

5. SUPPLEMENT(S)

NUMBER(S)	DATE(S)
S-004 R/S	2/20/79

6. NAME OF DRUG: Naprosyn Tablets

7. NONPROPRIETARY NAME: Naproxen

8. SUPPLEMENT(S) PROVIDES FOR:
The marketing of a 375 mg coated Naprosyn tablet

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES

10. PHARMACOLOGICAL CATEGORY: Anti-inflammatory

11. HOW DISPENSED: [X] RX [ ] OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S): Tablet

14. POTENCY *(ies)*: 125 mg and 250 mg

15. CHEMICAL NAME AND STRUCTURE
(+)-6-Methoxy- -methyl-Z-naphthaleneacetic acid

16. RECORDS AND REPORTS
CURRENT: [X] YES [ ] NO
REVIEWED: [X] YES [ ] NO

17. COMMENTS

This resubmission contains the firms response to our letter dated 1/21/79, in which the following points were requested on the 375 mg tablet.

1) Weight variation
2) Content uniformity
3)
4) Change specific
5) Change the dissolution limit

18. CONCLUSIONS AND RECOMMENDATIONS
The firm has agreed to all changes. The approval of this supplement awaits the results of the methods validation

7/11/79

RHWood/6/19/79 FT/eia/6/27/79

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
A. W. Coulter	A. W. Coulter	June 15, 1979

RHWood 7/5/79

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1.

ltr dtd 2/6/79

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Chemistry Review 2

CHEMIST'S REVIEW # (3)
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
DORDP	17-581

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Syntex Corporation
Palo Alto, California 94304

4. AF NUMBER
APR 0 3 1980

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S004	5-5-77

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Naprosyn	Naproxen

8. SUPPLEMENT(S) PROVIDES FOR:
A new strength - 375 mg naproxen per tablet

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
See the Attachments

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
NSAI	☒ RX ☐ OTC	—

13. DOSAGE FORM (S)	14. POTENCY *(ies)*
Tablets	250 mg (375 mg proposed)

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS
Chemist Review #1 dated 7-31-78 of Dr. A. Coulter. A definite conclusion for approval of S004 was not made because of pending — and bioavailability review. A rev/w.f. letter was issued on 1-21-79.
Since than, the applicant has made many changes as evident from 13 amendments, which are included in this review.
As of the date of this review, HFD-420 has not provided a report on methods validation.
The bioavailability review dated 12-3-79 is satisfactory under section 320-22 (d) (2) of 21 CFR.

18. CONCLUSIONS AND RECOMMENDATIONS
Issue an approvable letter when the following items are found satisfactory
a) — report b) updated EIR c) updated stability data for —
d) revised labeling e) production batch records (8H) or a commitment.

RD/endorsed/3/5/80 eia/ft/3/25/80

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
R. M. Patel	R M Patel 4-1-80	3/3/80

RKWood 4/1/80

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Chemistry Review 3

CHEMIST'S REVIEW #4 (If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)	1. ORGANIZATION	2. NDA NUMBER
	DORDP	17-581

3. NAME AND ADDRESS OF APPLICANT (City and State)

Snytex Laboratories
3401 Hillview Avenue
Palo Alto, CA 94304

4. AF NUMBER
MAY 30 1980

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S004	5/5/77

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Naprosyn	Naproxen

8. SUPPLEMENT(S) PROVIDES FOR:
A new Strength - film coated 375mg per tablet

9. AMENDMENTS AND OTHER (Reports, etc.) DATES
3-21-1980
3-31-1980 M.V.
4-11-1980 M.V.

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
NSAI	[X] RX [ ] OTC	

13. DOSAGE FORM (S)	14. POTENCY (ies)
Tablets	250mg (375mg proposed)

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT [ ] YES [ ] NO
REVIEWED [ ] YES [ ] NO

17. COMMENTS

1. A copy of the master batch record is provided for production of [redacted] 000 naprosyn film coated tablets.
2. Updated stability and dissolution data are provided ([redacted] respectively). As requested, available dissolution data on two batches are provided utilizing the latest dissolution method [redacted], which has been approved by our Division of Biopharmaceutics and validated by HFD-420 (Data by this method are satisfactory for 14 months and by the old method for 36 months) stability data support a 36-month expirating dating.
3. The draft copy of the package insert (02-272-42-9 of January 1980) is adequate for both Description and How Supplied sections.

18. CONCLUSIONS AND RECOMMENDATIONS

1. S004 is approvable from manufacturing and controls view point. A "SBA" will be written when the following is completed:
2. Since a comgined "package insert" is recommended by the Group leader, S004 cannot be approved separately until NDA 18-164 (Anaprox) is also processed together with this supplement.

HFD-150/HFD-150/RMPatel/R/D endorsed:RHWood: 4/28/80/F/T/an/5/8/80

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
R. M. Patel	RMPatel 5/13/80	4/24/80

RHWood 5/15/80

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wrp 5/19/80

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Chemistry Review 4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-581 / S-004

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Naproxen 375 mg tablet
(Naprosyn)
NDA 17-581/S004

Syntex Corporation
Palo Alto, California
Submission Dated:
August 31, 1979
October 25, 1979

REVIEW OF SUBMISSIONS

The firm requested a waiver for in vivo bioavailability requirements of 375 mg Naproxen based on 21 CFR 320.22 (d)(2) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product made by the same manufacturer and the following conditions are met:

(i) The bioavailability of this other drug product has been demonstratred.

(ii) Both drug products meet an appropriate in vitro test approved by the Food and Drug Administration.

(iii) The applicant submits evidence showing that both drug products are proportionally smiliar in their active and inactive ingredients."

OVERALL RECOMMENDATION:

A waiver of in vivo bioavailability study for 375 mg naproxen tablets based on 21 CFR 320.22 is approvable by the Division of Biopharmaceutics.

OVERALL COMMENTS:

The submissions met the following requirements as stated in 21 CFR 320.22 (d)(2) for a waiver of in vivo bioavailability study.

a. The bioavailability of 125 mg and 250 mg naproxen tablets has been demonstrated and approved (review dated 3/26/75).

b. The in vitro dissolution tests and specificaions for both 250 mg and 375 mg were appropriate and approved.

3. [redacted]

The following information was provided by the firm.

I) Data submitted in Aug. 31, 1979.

A. Formulations:

B. Dissolution Rate:

The dissolution test was conducted in pH 7.4 buffer by utilizing USP paddle method at 50 rpm. 12 Individual tablets were tested. The results (mean and standard deviation) presented as % of dissolved in 45 minutes are listed below.

250 mg	375 mg

In vivo bioavailability and in-vitro dissolution.(ICM #623)

OBJECTIVE:

To establish a manufacturing control range for the 250 mg naproxen tablet by comaring plasma levels from 3 tablets with different in vitro dissolution rates.

STUDY DESIGN:

This was a three-way randomized crossover design involving 2 healthy male volunteers of 21 to 55 years of age. Each subject received the following treatments after an overnight fast. There was a one week washout period separated between the treatments.

Treatment A - 250 mg naproxen tablet(Lot No. 48062, Production batch).

Treatment B - 250 mg naproxen tablet (Lot No. 3540 - 1272, research batch).

Treatment C - 250 mg naproxen tablet(Lot No. 3540 - 1271, research batch).

Blood samples were collected and naproxen concentrations in plasma was determined by gas chromatography.

FORMULATIONS:

A. 250 mg naproxen tablets (Lot # 48062)

B. Experimented 250 mg naproxen tablets (Lot No. 3540-1272)
The same formulation as A.The method of manufacturing same as (A) exept total amount of starch was added before

C. Expermental 250 mg naproxen tablet (Lot 3540-1271).

The same formulations and the same method of manufacturing as (B).

RESULTS:

1. Summary data (mean and standard deviation) for naproxen plasma levels and pharmacokinetic parameters:

Plasma level (mcg/ml)	A	B	C
0.33 hr.	6.9(10.8)	1.0(1.2)	0.9(1.6)
0.67	34.7(30.0)	5.1(2.2)	2.8(2.3)
1.00	52.9(36.1)	8.9(4.6)	5.5(3.4)
2	76.9(16.0)	49.8(20.8)	31.7(19.6)
4	63.3(12.3)	68.3(12.2)	58.7(17.8)
6	50.6(8.4)	55.4(9.4)	55.3(8.0)
8	42.5(8.3)	48.3(10.5)	49.1(7.0)
24	19.1(4.9)	20.8(5.3)	22.9(7.0)
48	7.8(3.1)	8.4(3.0)	8.4(3.2)
Cmax(mcg/ml)	80.5(16.0)	72.1(11.9)	64.1(10.7)
Tmax(hr)	2.1(1.0)	3.5(0.9)	4.5(1.2)
AUC(0-24 hr)	927(175)	931(171)	905(145)
AUC(0-8 hr)	435(81)	378(56)	329(63)

There were statistically significant differences for Cmax, Tmax, AUC (0-8 hours) and plasma levels at sampling times except at 4 hour and 48 hours after dosing.

There were no statistically significant differences for AUC (0-24 hours) and AUC (0-48 hours).

2. The dissolution tests were conducted in 600 ml of pH 7.4 buffer by USP paddle method at 50 rpm. Twelve individual tablets were tested. The summary data (mean and standard direction) was as following:

Percent of dose dissolved(%)

Time	A	B	C
15 min			
30			
45			
60			
120			

COMMENTS:

1. The study demonstrated that there were differences in the rate of absorption but not in the extent of absorption for naproxen among the tablets tested. The *in vivo* absorption rate was reflected by the *in vitro* dissolution rate.

Nora Chiang, Ph.D.
Pharmacokinetics Branch

cc: NDA17-581, HFD-150, HFD-525(Chiang), Drug file, Review file, Chron file.

NCHIANG/bes/12-3-79 (1958P)
RD INITIALED BY EDPURICH
FINAL TYPE INITIALED EDPURICH EDPurich 12/4/79

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Director
Division of Oncology & Radiopharmaceutical
Drug Products (HFD-150)
Attn: A. W. Coulter

DATE: January 23, 1979

FROM : Chief, Manufacturing Review Branch (HFD-322)
Division of Drug Manufacturing

SUBJECT: Approvable NDA 17-581/S-004 - Naprosyn, 375 mg., Tablets, 5/9/79

APPLICANT: Syntex Corporation
Palo Alto, CA.

MFR:	EI	QA PROFILE
Syntex Inc., Humacao, P.R.	2/78	3/78

We have evaluated the operations of Syntex Inc., Humacao, P.R. as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) for the subject pending application. We conclude that there is no reason to withhold approval of the subject application insofar as CGMP compliance of these firms is concerned for the type of operations as specified in this pending application.

Our evaluation is based in part on Establishment Inspection and/or Quality Assurance Profile information as referenced above.

David H. Bryant

David H. Bryant

cc: LOS-DO (HFR-9200)
SJN-DO (HFR=2400)
HFD-322 Firm File
HFD-300 R/F
HFD-150 (Dr. Grove)
HFD-150 (NDA Orig)

WAMatthews:ljh:1/23/79

JUN 24 1977

NDA 17-581

Syntex Corporation
Attention: James D. Mutch
Associate Director for Regulatory Affairs
3401 Hillview Avenue
Palo Alto, California 94304

Gentlemen:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Naprosyn® (naproxen) Tablets

NDA Number: 17-581

Supplement Number: S-004

Date of Supplement: May 5, 1977

Date of Receipt: May 9, 1977

All communications concerning this NDA should be addressed as follows:

Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM #17B-34
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

cc: SAN-DO
NDA Orig.
HFD-150
HFD-150/JMarks/6/20/77

SUPPLEMENT ACKNOWLEDGEMENT

JM 6/22/77
WJGyarfas 6/[illegible]/77

Naproxen
(Naprosyn)
375 mg tablets
NDA 17-581/S-004

Syntex Co.
Palo Alto, California
Submission Dated:
May 5, 1977
(ICM #529)

REVIEW OF A BIOEQUIVALENCE STUDY

INTRODUCTION:

Naproxen is a nonsteroidal anti-inflammatory agent related to arylacetic acid class. The purpose of this study was to compare the bioavailability of 375 mg Naproxen tablet to 3 of marketed 125 mg tablets.

STUDY DESIGN:

1. Twelve healthy subjects in Syntex Co. were involved in this study. This is a randomized crossover design with a one-week interval between the treatment.

2. Each subject was fasted overnight before the medication. The fast was continued for another 4 hours after the medication.

3. Each subject received 375 mg of Naproxen of the following formulations with 100 ml of water.

Formulations for the two tablets are:

	375 mg tablet	125 mg tablet
Naproxen	375.000 mg	125.000 mg
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

ANALYTICAL METHOD:

Naproxene is extracted with ether from plasma and methylated with diazomethane, then analyzed by gas chromatography using the methyl ester of 6-methoxy-2-naphthyl-acetic acid as internal reference standard. Assay was conducted at Syntex Co.

RESULTS:

1. Plasma data is presented:

	375 mg tablet	125 mg tablet X 3
Plasma level at	Mean (S.D.) mcg/ml	Mean (S. D.)
0 hr	0	0
0.33	17.3 (18.9)	2.7 (2.8)
0.67	40.0 (18.4)	13.2 (8.5)
1.0	47.0 (18.3)	24.2 (13.0)
2.0	48.3 (15.2)	53.2 (7.6)
4.0	42.0 (6.6)	42.7 (5.4)
6.0	34.0 (4.1)	34.2 (4.8)
8.0	28.0 (3.5)	28.8 (3.3)
24.0	12.2 (4.2)	12.7 (3.6)
48.0	4.2 (3.0)	4.7 (2.2)

Cmax mcg/ml	56.0 (10.9)	53.2 (7.6)
Tmax hr	1.92 (1.61)	2.0 (0.0)
AUC (0-8 hr) mcg/ml X hr	302.9 (52.0)	284.0 (30.4)
AUC (0 -∞) mcg/ml X hr	925.9 (271.5)	925.0 (205.9)
Terminal Half-lives hr	14.9 (3.70)	15.0 (3.74)

No significant differences were observed for Cmax, Tmax and AUC between the two formulations.

2. The dissolution rates of Naprosyn tablets were determined by vibrating the tablet in dissolution medium (pH = 4.8 buffer) which was constantly stirred. The dissolution rates specification for 125 mg tablets are to have no less than [redacted] dissolved in [redacted] minutes. The data (mean and standard deviation) for 375 mg is:

	No. of samples	% dissolved
15 minutes	6	77.5 ± 3.9
30 minutes	7	88.2 ± 2.2
45 minutes	7	96.8 ± 3.5
60 minutes	7	99.8 ± 3.6

RECOMMENDATION:

The bioequivalence of Naproxene 375 mg is demonstrated with 3 of 125 mg marketed Naproxen tablets in vivo, however, the firm should be informed of comment #1.

COMMENTS:

1. The in vitro dissolution tests are different from the current FDA dissolution methodology (USP dissolution method I or II). The firm should justify for their dissolution method used and attempt to develop an in vitro dissolution method to correlate with its in vivo bioavailability.

2. Larger intersubject variations in times to achieve peak plasma

concentration are observed for 375 mg tablets. However, there is no statistically significant differences in peak concentrations and AUCs between the two products.

3. The half-lives presented were consistent with the previous studies.

Nora Chiang, Ph.D.
Biopharmaceutics Review Branch

cc: NDA Orig., HFD-150, HFD-522, HFD-525, Chron File

NCHIANG/mrs/2/5/79 ([redacted])
RD INITIALED BY EDPURICH
FINAL TYPE INITIALED BY JPSKELLY

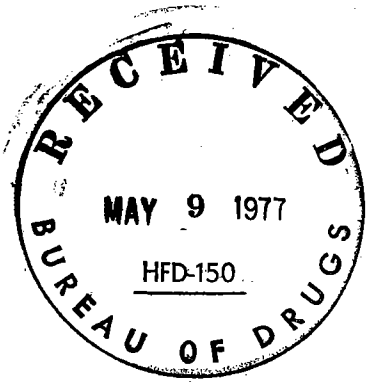
SYNTEX CORPORATION
3401 HILLVIEW AVENUE
PALO ALTO, CALIF. 94304

REGULATORY AFFAIRS

Noted ORN 4-2[illegible]
To Chemist
FPL

NDA NO. 17581 REF. NO. 5004
NDA SUPPL FOR Manuf. Change

May 5, 1977



Division of Oncology and Radio-
pharmaceutical Drug Products
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 17-581
NAPROSYN® (naproxen) Tablets

Gentlemen:

Enclosed is a supplemental application providing data to permit the marketing of a 375 mg. NAPROSYN tablet. Enclosed information includes the following:

1. A clinical study showing the bioequivalence of the proposed 375 mg. tablet and the approved 125 mg. tablet.

2. Complete information on the manufacturing and control of the 375 mg. tablet.

3. Labels and labeling.

All other information previously submitted in this NDA is unchanged from that currently approved.

Your early review and approval of this supplement application will be greatly appreciated.

Sincerely,

SYNTEX CORPORATION

James D. Mutch
Associate Director
Regulatory Affairs
(415) 855-5436

JDM:dw
Enclosures

CERTIFIED MAIL
Return Receipt Requested