CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 75061

Trade Name Naproxen Delayed-release Tablets 375mg and 500mg

Generic Name Naproxen Delayed-release Tablets 375mg and 500mg

Sponsor Invamed, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 75061

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75061

APPROVAL LETTER

ANDA 75-061

FEB 18 1998

Invamed, Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130 North
Dayton, New Jersey 08810

Dear Sir:

This is in reference to your abbreviated new drug application dated January 27, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Naproxen Delayed-release Tablets, 375 mg and 500 mg.

Reference is also made to your amendments dated July 29, October 8, November 25, December 16, 1997; and January 14, and January 23, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Naproxen Delayed-release Tablets, 375 mg and 500 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (EC-Naprosyn® Delayed-release Tablets, 375 mg and 500 mg, respectively, of Syntex FP, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours.

2/18/98

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75061

FINAL PRINTED LABELING

NDC 52189-290-30

invamed inc.

Naproxen Delayed-release Tablets

500 mg

(Enteric Coated Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

EACH ENTERIC COATED TABLET CONTAINS:
Naproxen ..... 500 mg

USUAL DOSAGE: See accompanying prescribing information for complete details.

Keep this and all drugs out of the reach of children.

Dispense in a well-closed, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-290-30 8

Lot No.:
Exp. Date:

MF # 1148

NAPROXEN DELAYED-RELEASE TABLETS,
375 mg and 500 mg
ANDA # 75-061
MINOR AMENDMENT
(RESPONSE TO FDA FAX DATED 09/23/97)

NDC 52189-290-24

invamed inc.

Naproxen Delayed-release Tablets

500 mg

(Enteric Coated Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH ENTERIC COATED TABLET CONTAINS:
Naproxen ..... 500 mg

USUAL DOSAGE: See accompanying prescribing information for complete details.

Keep this and all drugs out of the reach of children.

Dispense in a well-closed, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-290-24 7

Lot No.:
Exp. Date: FEB 18 1998
MF # 1147

300050

NAPROXEN DELAYED-RELEASE TABLETS,
375 mg and 500 mg
ANDA # 75-061
MINOR AMENDMENT
(RESPONSE TO FDA FAX DATED 09/23/97)

NDC 52189-289-30

invamed inc.

Naproxen Delayed-release Tablets

375 mg

(Enteric Coated Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

EACH ENTERIC COATED TABLET CONTAINS:
Naproxen ..... 375 mg

USUAL DOSAGE: See accompanying prescribing information for complete details.

Keep this and all drugs out of the reach of children.

Dispense in a well-closed, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-289-30 2

Lot No.:
Exp. Date:

MF # 1146

J00044

NAPROXEN DELAYED-RELEASE TABLETS,
375 mg and 500 mg
ANDA # 75-061
MINOR AMENDMENT
) FDA FAX DATED 09/23/97)

NDC 52189-289-24

invamed inc.

Naproxen Delayed-release Tablets

375 mg

(Enteric Coated Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH ENTERIC COATED TABLET CONTAINS:
Naproxen ..... 375 mg

USUAL DOSAGE: See accompanying prescribing information for complete details.

Keep this and all drugs out of the reach of children.

Dispense in a well-closed, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-289-24 1

Lot No.:
Exp. Date: FEB 18 1998

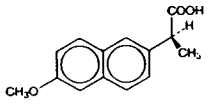
MF # 1145

300049

NAPROXEN DELAYED-RELEASE TABLETS

DESCRIPTION: Naproxen is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs.

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



Molecular Formula: $C_{14}H_{14}O_3$

MW = 230.26

Naproxen is a practically 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. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8.

Each enteric-coated tablet, for oral administration, contains 375 mg or 500 mg of naproxen. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer, polyethylene glycol, povidone, talc and triacetin. The imprinting ink contains the colorant FD&C Red No. 40-aluminum lake.

The dissolution of this enteric-coated naproxen tablet is pH dependent with rapid dissolution above pH 6. There is no dissolution below pH 4.

CLINICAL PHARMACOLOGY: Naproxen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.

Pharmacokinetics: Naproxen itself is rapidly and completely absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95%. The elimination half-life of naproxen ranges from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days and the degree of naproxen accumulation is consistent with this half-life.

Absorption: Naproxen delayed-release tablets are designed with a pH-sensitive coating to provide a barrier to disintegration in the acidic environment of the stomach and to lose integrity in the more neutral environment of the small intestine. The enteric polymer coating selected for naproxen delayed-release tablets dissolves above pH 6. When naproxen delayed-release tablets were given to fasted subjects, peak plasma levels were attained about 4 to 6 hours following the first dose (range 2 to 12 hours). An *in vivo* study in man using radiolabeled naproxen delayed-release tablets demonstrated that naproxen delayed-release tablets dissolve primarily in the small intestine rather than the stomach, so the absorption of the drug is delayed until the stomach is emptied.

When 500 mg of naproxen delayed-release tablets were given twice a day to fasted subjects (n=24), the following was observed after 1 week of dosing:

C_{max} (mcg/mL)	94.9 (18%)*
T_{max} (hours)	4 (39%)*
$AUC_{0\text{-}12\ hr}$ (mcg-hr/mL)	845 (20%)*

*mean value (coefficient of variation)

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*mean value (coefficient of variation)

Antacid Effects: When naproxen delayed-release tablets was given as a single dose with antacid (54 mEq buffering capacity), the peak plasma levels of naproxen were unchanged, but the time to peak was reduced (mean T_{max} fasted 5.6 hours, mean T_{max} with antacid 5 hours), although not significantly.

Food Effects: When naproxen delayed-release tablets were given as a single dose with food, peak plasma levels in most subjects were achieved in about 12 hours (range 4 to 24 hours). Residence time in the small intestine until disintegration was independent of food intake. The presence of food prolonged the time the tablets remained in the stomach, time to first detectable serum naproxen levels, and time to maximal naproxen levels (T_{max}), but did not affect peak naproxen levels (C_{max}).

Distribution: Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen). However, the concentration of unbound naproxen continues to increase proportionally to dose.

Metabolism: Naproxen is extensively metabolized to 6-*O*-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes.

Elimination: The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-*O*-desmethyl naproxen (less than 1%) or their conjugates (66-92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure metabolites may accumulate.

Special Populations:

Children: In children of 5 to 16 years of age with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen oral suspension were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in children and adults. Pharmacokinetic studies of naproxen were not performed in children of less than 5 years of age. Naproxen delayed-release tablets have not been studied in subjects under the age of 18.

Renal Insufficiency: Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites, and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency.

Clinical Studies: *General Information:* Naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis. Improvement in patients treated for rheumatoid arthritis was demonstrated by a reduction in joint swelling, 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. Generally, response to naproxen has not been found to be dependent on age, sex, severity or duration of rheumatoid arthritis.

In patients with osteoarthritis, the therapeutic action of naproxen 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, osteoarthritis and juvenile arthritis, naproxen has been shown to be comparable to aspirin and indomethacin 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 in naproxen treated patients than in those treated with aspirin or indomethacin.

In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.

Naproxen 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 naproxen has a "steroid-sparing" effect has not been adequately studied. When

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Naproxen 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 naproxen has a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs the combination may result in higher frequency of adverse events than demonstrated for either product alone.

Three 6-week, double-blind multicenter studies with naproxen delayed-release tablets (375 or 500 mg BID, n=385) and naproxen immediate-release tablets (375 or 500 mg BID, n=279) were conducted comparing naproxen delayed-release tablets with naproxen immediate-release tablets including 355 rheumatoid arthritis and osteoarthritis patients who had a recent history of NSAID related GI symptoms. These studies indicated that naproxen delayed-release tablets and naproxen immediate-release tablets showed no significant differences in efficacy or safety and had similar prevalence of minor GI complaints. Individual patients, however, may find one formulation preferable to the other.

Five hundred and fifty-three patients received naproxen delayed-release tablets during long-term open label trials (mean length of treatment was 159 days). The rates for clinically-diagnosed peptic ulcers and GI bleeds were similar to what has been historically reported for long-term NSAID use.

Individualization of Dosage: Because naproxen delayed-release tablets dissolve in the small intestine rather than in the stomach, the absorption of the drug is delayed compared to the other naproxen formulations (see CLINICAL PHARMACOLOGY).

The recommended strategy for initiating therapy is to choose a formulation and a starting dose likely to be effective for the patient and then adjust the dosage based on observation of benefit and/or adverse events. A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients (see PRECAUTIONS).

Osteoarthritis/Rheumatoid Arthritis/Ankylosing Spondylitis: The recommended dose of naproxen delayed-release tablets is 375 mg or 500 mg taken twice daily. During long-term administration the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. In patients who tolerate lower doses well, the dose may be increased to 1500 mg per day when a higher level of anti-inflammatory/analgesic activity is required. When treating patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefit to offset the potential increased risk. The morning and evening doses do not have to be equal in size and administration of the drug more frequently than twice daily does not generally make a difference in response (see CLINICAL PHARMACOLOGY).

Juvenile Arthritis: The use of naproxen oral suspension allows for more flexible dose titration.

The recommended total daily dose is approximately 10 mg/kg given in 2 divided doses (i.e., 5 mg/kg given twice a day) (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE: Naproxen delayed-release tablets are indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and juvenile arthritis. Naproxen oral suspension is recommended for juvenile rheumatoid arthritis in order to obtain the maximum dosage flexibility based on the child's weight.

Naproxen delayed-release tablets are not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen containing products (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS: Naproxen is contraindicated in patients who have had allergic reactions to prescription as well as to over-the-counter products containing naproxen. It is also contraindicated in patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps. Both types of reactions have the potential of being fatal. Anaphylactoid reactions to naproxen, whether of the true allergic type or the pharmacologic idiosyncratic (e.g., aspirin hypersensitivity syndrome) type, usually but not always occur in patients with a known history of such reactions. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and

doses (i.e., 5 mg/kg given twice a day) (see DOSAGE AND ADMINISTRATION).

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WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy: Serious gastrointestinal toxicity such as bleeding, ulceration and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date with all naproxen products have not identified any subset of patients not at risk of developing peptic ulceration and bleeding or any differences between naproxen products in their propensity to cause peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: NAPROXEN DELAYED-RELEASE TABLETS SHOULD NOT BE USED CONCOMITANTLY WITH OTHER NAPROXEN CONTAINING PRODUCTS SINCE THEY ALL CIRCULATE IN THE PLASMA AS THE NAPROXEN ANION.

If the steroid dose is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients should 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 periodically.

The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed non-infectious, non-inflammatory painful conditions.

Because of adverse eye findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of naproxen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria and occasionally nephrotic syndrome associated with naproxen containing products and other NSAIDs since they have been marketed.

A second form of renal toxicity has been seen in patients taking naproxen as well as other nonsteroidal anti-inflammatory drugs. In patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is typically followed by recovery to the pretreatment state.

Naproxen and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with caution in

dyspepsia associated with nonsteroidal anti-inflammatory drugs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment should be discontinued.

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A second form of renal toxicity has been seen in patients taking naproxen as well as other nonsteroidal anti-inflammatory drugs. In patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is typically followed by recovery to the pretreatment state.

Naproxen and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with caution in

patients with significantly impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. Caution should be used if the drug is given to patients with creatinine clearance of less than 20 mL/minute because accumulation of naproxen metabolites has been seen in such patients.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Hepatic Function: As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with naproxen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), naproxen should be discontinued.

Fluid Retention and Edema: Peripheral edema has been observed in some patients receiving naproxen.

Information for Patients: Naproxen, like other drugs of this class, is not free of side effects. The side effects can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections) and likely benefits of naproxen treatment, particularly when it is used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

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

Laboratory Tests: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow patients chronically treated with naproxen for signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up and what they should do if certain signs and symptoms do appear (see WARNINGS - Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy).

Drug Interactions: The use of NSAIDs in patients who are receiving ACE inhibitors may potentiate renal disease states (see PRECAUTIONS, Renal Effects).

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 (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

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 nonsteroidal 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 (see CLINICAL PHARMACOLOGY, Clinical Studies, General Information).

Concomitant administration of naproxen and aspirin is not recommended because naproxen is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations and peak plasma levels.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported. Naproxen and other nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers.

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

Caution should be used if naproxen is administered concomitantly with methotrexate. Naproxen and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.

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Caution should be used if naproxen is administered concomitantly with methotrexate. Naproxen and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.

Due to the gastric pH elevating effects of H_2-blockers, sucralfate, and intensive antacid therapy, concomitant administration of naproxen delayed-release tablets is not recommended.

Drug/Laboratory Test Interactions: Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene 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 naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen 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 naproxen at doses of 8, 16 and 24 mg/kg/day (50, 100 and 150 mg/m^2). The maximum dose used was 0.28 times the systemic exposure to humans at the recommended dose. No evidence of tumorigenicity was found.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m^2/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m^2/day, 0.27 times the human systemic exposure), and mice at 170 mg/kg/day (510 mg/m^2/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naproxen should not be used during pregnancy unless clearly needed.

Non-teratogenic Effects: There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants. Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use during third trimester should be avoided.

Nursing Mothers: The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for juvenile arthritis are based on well-controlled studies (See DOSAGE AND ADMINISTRATION). There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in juvenile arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg (as naproxen oral suspension, see DOSAGE AND ADMINISTRATION section), with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

ADVERSE REACTIONS: The following adverse reactions are divided into three parts based on frequency and whether or not the possibility exists of a causal relationship between naproxen and these adverse events. In those reactions listed as "Probable Causal Relationship" there is at least one case for each adverse reaction where there is evidence to suggest that there is a causal relationship between drug usage and the reported event.

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily

that found in the plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

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Adverse reactions reported in controlled clinical trials in 968 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen (see CLINICAL PHARMACOLOGY).

In controlled clinical trials with about 80 children and in well monitored open-label studies with about 400 children with juvenile arthritis, treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in children than in adults.

The following adverse reactions are divided into three parts based on frequency and causal relationship.

Incidence Greater Than 1% (Probable Causal Relationship)

Gastrointestinal: constipation*, heartburn*, abdominal pain*, nausea*, dyspepsia, diarrhea, and stomatitis.

Central Nervous System: headache*, dizziness*, drowsiness*, lightheadedness, and vertigo.

Dermatologic: itching (pruritus)*, 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. Those reactions observed through voluntary reporting since marketing are italicized.

Gastrointestinal: Abnormal liver function tests, colitis, gastrointestinal bleeding and/or *perforation, hematemesis,* jaundice, pancreatitis, melena, vomiting.

Renal: Glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis.

Hematologic: Agranulocytosis, *eosinophilia, granulocytopenia, leukopenia,* thrombocytopenia.

Central Nervous System: Depression, dream abnormalities, inability to concentrate, *insomnia, malaise, myalgia,* and *muscle weakness.*

Dermatologic: Alopecia, photosensitive dermatitis, urticaria, skin rashes, *photosensitivity reactions resembling porphyria cutanea tarda and epidermolysis bullosa.*

Special Senses: Hearing impairment.

Cardiovascular: Congestive heart failure.

Respiratory: Eosinophilic pneumonitis.

General: Anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever).

Incidence Less Than 1% (Causal Relationship Unknown)

These observations are being listed to serve as alerting information to the physician.

Hematologic: Aplastic anemia, hemolytic anemia.

Central Nervous System: Aseptic meningitis, cognitive dysfunction.

Dermatologic: Epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome.

Gastrointestinal: Non-peptic gastrointestinal ulceration, ulcerative stomatitis.

Cardiovascular: Vasculitis.

General: Hyperglycemia, hypoglycemia.

OVERDOSAGE: Significant naproxen overdosage may be characterized by drowsiness, heartburn, indigestion, nausea or vomiting. A few patients have experienced seizures, but it is not clear whether or not these were drug related. 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 1500 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. In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen. Hemodialysis does not decrease the

9

Dermatologic: Alopecia, photosensitive dermatitis, urticaria, skin rashes, photosensitivity reactions resembling porphyria cutanea tarda and epidermolysis bullosa.

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Should a patient ingest a large number of tablets, accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

DOSAGE AND ADMINISTRATION:

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis: The recommended dose of naproxen delayed-release tablets is 375 mg or 500 mg twice daily. To maintain the integrity of the enteric coating, the tablet should not be broken, crushed, or chewed during ingestion.

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. 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.

In patients who tolerate lower doses well, the dose may be increased to naproxen 1500 mg per day for limited periods when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefits to offset the potential increased risk (see CLINICAL PHARMACOLOGY and Individualization of Dosage).

Juvenile Arthritis: The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses (i.e., 5 mg/kg given twice a day). Naproxen tablets are not well suited to this dosage so use of naproxen oral suspension is recommended for this indication.

HOW SUPPLIED:

Naproxen delayed-release tablets 375 mg are white, capsule-shaped, film-coated, unscored, imprinted with INV 289 in red color on one side are supplied as follows:

NDC 52189-289-24 in bottles of 100 tablets
NDC 52189-289-30 in bottles of 1000 tablets

Naproxen delayed-release tablets 500 mg are white, capsule-shaped, film-coated, unscored, imprinted with INV 290 in red color on one side are supplied as follows:

NDC 52189-290-24 in bottles of 100 tablets
NDC 52189-290-30 in bottles of 1000 tablets

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Dispense in a well-closed, light-resistant container, as defined in the USP.

CAUTION

Federal law prohibits dispensing without prescription.

Manufactured by
INVAMED INC.
2400 Route 130
Dayton, NJ 08810, USA

Date of Revision: September 1997
L-1252; MF# 1149A

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75061

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-061

3. NAME AND ADDRESS OF APPLICANT
Invamed Inc.
Attention: Mahendra Patel
2400 Route 130
Dayton, NJ 08810

4. LEGAL BASIS FOR SUBMISSION
Approved Product EC-Naprosyn Tablets of Syntex Puerto Rico Inc.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Naproxen

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original Application Submission Date January 27, 1997
"Refuse To File" Letter Issue Date April 22, 1997
Amendment Date April 29, 1997
Acceptable For Filing Date April 30, 1997
Amendment Date October 8, 1997
Telephonic Amendment Date December 16, 1997
Telephone Amendment Date January 14, 1998

10. PHARMACOLOGICAL CATEGORY
Anti-inflammatory

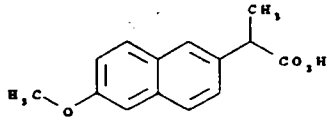
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Delayed Release Tablet

14. POTENCY
375 mg and 500 mg

15. CHEMICAL NAME AND STRUCTURE
Naproxen USP
$C_{14}H_{14}O_3$; M.W. = 230.26



(+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid.
CAS [22204-53-1]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
See Individual Review Sections; Comments from deficiency letter are followed by firm's response.

18. CONCLUSIONS AND RECOMMENDATIONS
CMC & Labeling Approvable, Bio Pending

19. REVIEWER:
U.S. Atwal

DATE COMPLETED:
December 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75061

BIOEQUIVALENCE REVIEW(S)

Naproxen Delayed-Release Tablets, USP
375 mg and 500 mg Tablets
ANDA #75-061
Reviewer: A.P.Patel
File:x\wpfile\biofinal\75061a.197

Invamed, Inc.
Dayton, NJ
Submission Date:
Jan. 1, 1997
July 30, 1997
Nov. 25, 1997

Review of an Amendment

The firm has submitted an amendment for review of dissolution data.

Deficiencies/comments reported to the firm:

1. The firm should tabulate lag and Tmax-adjusted (Tmax - lag) time for test and reference formulation.

Response: Tabulation of Lag and adjusted Tmax is provided.

2. The firm should tabulate integrity of test and reference tablets during the acid phase of dissolution testing.

Response: The integrity of tablets in the acid stage of the dissolution test is reported with dissolution data tables.

3. The firm has conducted dissolution test for test and reference tablets under differing volume and buffer conditions. The firm was requested to conduct dissolution test as described in USP 23, on July 18, 1997. The dissolution data submitted were unacceptable.

   The firm has conducted dissolution test under following conditions:
   Acid stage for Test and Reference tablets was conducted in 900 ml of 0.1 N HCL

   For 375 mg tablets: Test with 900 ml of 0.1 M potassium phosphate, pH 6.8

   Reference with 900 ml of 0.5 M potassium phosphate, pH 6.8

   For 500 mg tablets: Test with 900 ml of 0.1 M sodium phosphate buffer, pH 7.4.

   Reference with 900 ml of 0.1 M potassium phosphate buffer, pH 6.8

The volume of the acid or the buffer does not correspond to USP 23 methods described on pages 1795 - 96.

The firm should specify whether Method A or B was used for dissolution and appropriate interpretation of the results based on method of choice.

Response:

The firm has conducted dissolution testing as per USP23, pp1795-6, methods A and B.

The firm is implementing use of USP23 method B as a method of choice based on 'F_2' analysis of method A and B data.

Comments:

1. Dissolution data are acceptable as per USP23 method B (see attachment).

   In general, in a non USP method, percent of naproxen dissolved in 900 ml of sodium phosphate media of pH 7.4 is greater than that dissolved in buffered media of pH 6.8, except for 375mg test naproxen tablet (see attached graphs).

2. The integrity of tablets in the acid stage of the dissolution test is reported with dissolution data tables (see attachment).

3. Firm has submitted Lag and adjusted Tmax data (see attachment).

Recommendation:

1. The single-dose bioequivalence study #P96-366 conducted under fasting conditions by Invamed Pharmaceuticals, on its Naproxen 375 mg Tablets (Lot# D960901) comparing it to EC-Naprosyn^R 375 mg Tablets (Lot# 05118) manufactured by Syntex, is found to be acceptable by the Division of Bioequivalence. The study demonstrates that Invamed's Naproxen Tablet, 375 mg is deemed bioequivalent to the reference product, EC-Naprosyn^R Tablets, 375 mg, manufactured by Syntex.

2. The single-dose bioequivalence studies #P96-296 conducted under fasting conditions and #P96-343 conducted under non fasting conditions by Invamed Pharmaceuticals, on its Naproxen 500 mg Tablets (Lot# D960802) comparing it to EC-

Naprosyn ^{R} 500 mg Tablets (Lot# B0893) manufactured by Syntex, are found to be acceptable by the Division of Bioequivalence. The studies demonstrate that Invamed's Naproxen 500 mg Tablet, is deemed bioequivalent to the reference product EC-Naprosyn^{R} 500 mg Tablet, manufactured by Syntex.

3. The dissolution testing conducted by Invamed Pharmaceuticals, on its Naproxen 375 mg tablets (Lot# D960901) and 500 mg tablets (Lot# D960802), is acceptable. The formulation for the 375 mg strength is proportionally similar to the 500 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of *in vivo* non-fasting bioequivalence study requirements for the test 375 mg tablet is granted. The Division of Bioequivalence deems Naproxen Tablet, 375 mg, manufactured by Invamed Pharmaceuticals to be bioequivalent to EC-Naprosyn^{R} Tablet, 375 mg, manufactured by Syntex.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of acid and buffer phases (USP<724> Method B) at 37^{0}C using USP 23 apparatus 2 (paddle) at 50 RPM. The test drug should meet the following specifications:

   I. Not more than of the labeled amount of the drug in the dosage form is dissolved in 120 minutes under 0.1 N HCL acid phase.

   II. Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes under buffer phase, pH 6.8.

5. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing.

The firm should be informed of the recommendation.

A.P.Patel
Division of Bioequivalence
Review Branch III

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75061

ADMINISTRATIVE DOCUMENTS

ANDA **75-061** APPROVAL SUMMARY

DRUG PRODUCT: Naproxen Delayed-release Tablets, 375 mg and 500 mg

FIRM: Invamed Inc.

DOSAGE FORM: Delayed-release Tablet

STRENGTH: 375 mg and 500 mg

cGMP STATEMENT/EIR UPDATE STATUS: EER Acceptable Date July 15, 1997

BIO STUDY: PENDING

VALIDATION: DS is compendial; DP is not compendial (Validation PENDING)

*STABILITY:*Three months accelerated, 40°C (75% RH), and three months ambient condition, 25°C-30°C, data in the market package size, 100's and 1000's, provided. The container/closure system used for the stability study is equivalent to the system proposed for commercial use. All reported data are within specifications as listed. Thus, a 24 month expiration date is justified.

LABELING: APPROVE, Review Date October 16, 1997

STERILIZATION VALIDATION: (IF APPLICABLE): N/A

*SIZE OF BIO BATCH:*The bio batches, 375 mg (#D960901, tablets) and 500 mg (#D960802, tablets) are also test batches (drug substance source.

SIZE OF STABILITY BATCHES: Stability batches are the same as test batches (bio batches), ie #D960901 (375 mg) and #D960802 (500 mg).

PROPOSED PRODUCTION BATCHES: The proposed production batch size for each tablet strength is The manufacturing process for production batches is the same as that for test batches.

CHEMIST: **DATE:** 12/30/97

SUPERVISOR: **DATE:**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75061

CORRESPONDENCE

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-061 APPLICANT:Invamed Inc.

DRUG PRODUCT:Naproxen Delayed Release 375mg and 500mg Tablets USP

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

January 14, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA [illegible]

N/AM

Re: **NAPROXEN DELAYED-RELEASE TABLETS, 375 mg and 500 mg**
ANDA # 75-061
TELEPHONIC AMENDMENT

Dear Sirs

As per Dr. Dave's telephonic conversation with Mr. James Wilson, Project Manager, OGD dated January 14, 1998 and as instructed by Mr. Wilson, I have herewith enclosed a "*TELEPHONIC AMENDMENT*" document to our pending application for **NAPROXEN DELAYED-RELEASE TABLETS, 375 mg and 500 mg (ANDA # 75-061)** as required under 21 CFR 314.120 (submitted in duplicate).

As recommended, the firm has incorporated following control for dissolution testing during initial release of the drug product as well as monitoring of on-going stability studies:

Method: USP 23 [724], Method B; Apparatus 2, 50 rpm
Media: Stage I : 1000 mL of 0.1 N Hydrochloric Acid
Stage II: 1000 mL of 0.20 M Sodium Phosphate Buffer: 0.1 N HCl (1:3), pH 6.8 ± 0.05
Specifications: Stage I : NMT dissolved in 120 minutes
Stage II: NLT (Q) dissolved in 45 minutes

A copy each of Product Specifications and Release Report as well as amended stability protocols depicting the implementation of this control are attached herewith for ease of review.

The firm has submitted an additional copy of this Telephonic Amendment to the U.S. Food and Drug Administration, New Jersey District Office. We hereby certify that this additional copy (field copy) is a true copy of the Archival and Review copies of the Telephonic Amendment.

RECEIVED

JAN 15 1998

GENERIC DRUGS

Sincerely

Mahendra Patel, Ph.D.
Vice President

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

December 16, 1997

NDA ORIG AMENDMENT

N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **NAPROXEN DELAYED-RELEASE TABLETS,**
375 mg and 500 mg
ANDA # 75-061
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The firm has submitted an additional copy of this Telephonic Amendment to the U.S. Food and Drug Administration, New Jersey District Office. We hereby certify that this additional copy (field copy) is a true copy of the Archival and Review copies of the Telephonic Amendment.

Sincerely

Mahendra Patel, Ph.D.
Vice President

RECEIVED
DEC 17 1997
GENERIC DRUGS

12-19

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

FR

NDA ORIG AMENDMENT

N/AM

October 8, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **NAPROXEN DELAYED-RELEASE TABLETS,**
375 mg and 500 mg
ANDA # 75-061
MINOR AMENDMENT

Dear Sirs

I have herewith enclosed a "*MINOR AMENDMENT*" document to our pending application for **NAPROXEN DELAYED-RELEASE TABLETS, 375 mg and 500 mg (ANDA # 75-061)** as required under 21 CFR 314.120 (submitted in duplicate).

The firm has submitted an additional copy of this Minor Amendment to the U.S. Food and Drug Administration, New Jersey District Office. We hereby certify that this additional copy (field copy) is a true copy of the Archival and Review copies of the Minor Amendment.

Sincerely

M. Patel

Mahendra Patel, Ph.D.
Vice-President

RECEIVED
OCT 0 9 1997
GENERIC DRUGS

Marked

ANDA 75-061

Invamed Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130
Dayton, NJ 08810

JUN 2 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated April 22, 1995 and your amendment dated April 29, 1997. In addition we refer to your correspondence dated May 19, 1997

NAME OF DRUG: Naproxen Delayed-release Tablets, 375 mg and 500 mg

DATE OF APPLICATION: January 27, 1997

DATE OF RECEIPT: January 28, 1997

DATE ACCEPTABLE FOR FILING: April 30, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.
Should you have questions concerning this application, contact:

James Wilson

Project Manager
(301) 827-5849

Sincerely yours,

Jerry Phillips 6/2/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

invamed inc.

908-274-2400 Fax: 908-274-8989

2400 Rt. 130 North, Dayton, New Jersey 08810

April 29, 1997

Ms. Cecelia Parise
Project Manager
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
1c

Re: **ANDA # 75-061**
NAPROXEN DELAYED-RELEASE TABLETS
(375 mg and 500 mg strengths)

Dear Ms. Parise

We refer to a letter received dated April 22, 1997, indicating your decision for refusal to file this ANDA in accordance with 21 CFR 314.101(d) (3) and 314.127(8) (i).

We disagree with this decision and request an informal conference on May 16, 1997. Through this letter, we are also authorizing the following to represent Invamed Inc. on the issues referenced in your letter:

GENERIC DRUGS

We request you to resolve this issue in an expedited fashion. If the subject matter is resolved based on the provided information, we request you to honor the filing date as the date of acceptance and not April 22, 1997.

Sincerely,

M. N. Patel.

Mahendra Patel, Ph.D.
Vice President

ANDA 75-061

Invamed Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130
Dayton, NJ 09910

APR 22 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated January 27, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Naproxen Delayed-Release Tablets, 375 mg and 500 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> Your formulation includes the inactive ingredient in a quantity higher than has been previously approved by the agency. FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an abbreviated new drug application under 21 CFR paragraph (a)(8)(I) if, on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety. Examples of the changes that may raise serious questions of safety include, but are not limited to the following: A change in the composition to include a significantly greater content of an inactive ingredient than previously approved by the agency [21 CFR 314.127(8)(i)]. Therefore, your proposed product cannot be approved as an ANDA.
>
> Please provide additional justification to demonstrate the safety of the inactive ingredient uch as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range. Please either provide this documentation or reformulate your drug product.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in

writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Cecelia Parise

Project Manager
(301) 594-0315

Sincerely yours,

Jerry Phillips 4/22/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-061
cc: DUP/Jacket
Division File
HFD-92
Field Copy
HFD-600/Reading File
HFD-610/JPhillips
HFD-615/MBennett
Endorsement: HFD-615/PRickman, Chi date 4/22/97
HFD-615/CParise, CSO date 4/16/97
HFD-623/VSayeed, Chem Brancn I date
WP File x:\new\firmsam\invamed\ltrs&rev\75061.rtf
F/T File tdb 04-16-97
ANDA Refuse to File!

Application was found in Office at over 60 days. Was expedited review. The review for acceptability exceeds the 60 day Regulatory period.

invamed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

January 27, 1997

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: **Original ANDA Submission for**
NAPROXEN DELAYED-RELEASE TABLETS
(375 mg and 500 mg strengths)

Dear Sirs

I have herewith enclosed the original Abbreviated New Drug Application (ANDA) document for ***NAPROXEN DELAYED-RELEASE TABLETS (375 mg and 500 mg strengths).*** The ANDA application contains the following documents:

1.	Archival Copy	12 volumes
2.	Review Copy Chemistry, Manufacturing and Controls	4 volumes
3.	Review Copy Bioavailability/Bioequivalence (Hard copy of Raw Data with a copy of raw data on 3½" disk, attached to the inner cover)	8 volumes

4. Two additional separately bound copies of **Section XV (Controls for the Finished Dosage Form)** and **Section XVI (Analytical Methods); Page(s) 4749 through 5659** as the drug product is not a compendial article.

The firm has submitted an additional copy of the Technical Section [as required under 314.50 (d) (1)] to the U.S. Food & Drug Administration, New Jersey District Office. We hereby certify that this additional copy (field copy) is a true copy of the Technical Section as described in § 314.94 (a) (9) contained in the Archival and Review copies of the abbreviated application.

RECEIVED
JAN 20 1997
GENERIC DRUGS

Sincerely,

Mahendra Patel, Ph.D.
Vice President