CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-851

APPROVAL LETTER

ANDA 75-851

AUG 17 2001

Mylan Pharmaceuticals, Inc.
Attention: Frank Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated April 28, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Oxaprozin Tablets, 600 mg.

Reference is also made to your amendments dated September 5, and October 6, 2000, and July 20, 2001.

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 Oxaprozin Tablets, 600 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Daypro® Tablets 600 mg, of G.D. Searle and Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

...t-marketing reporting requirements for this abbreviated ...lication are set forth in 21 CFR 314.80-81 and 314.98. The ...ce of Generic Drugs should be advised of any change in the ...eting status of this drug.

...uest that you submit, in duplicate, any proposed ...ising or promotional copy, which you intend to use in your 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-40). 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-40) 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,

Robert L. Lest / for 8/17/2001

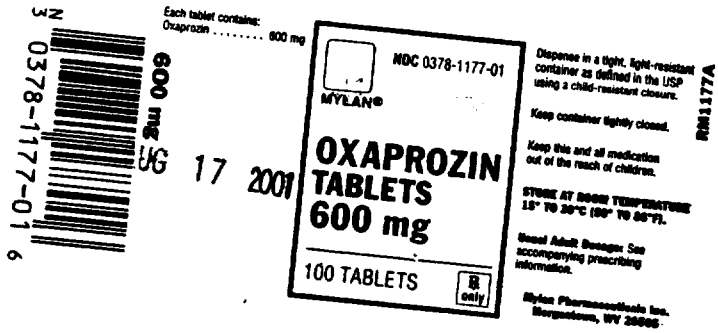
Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

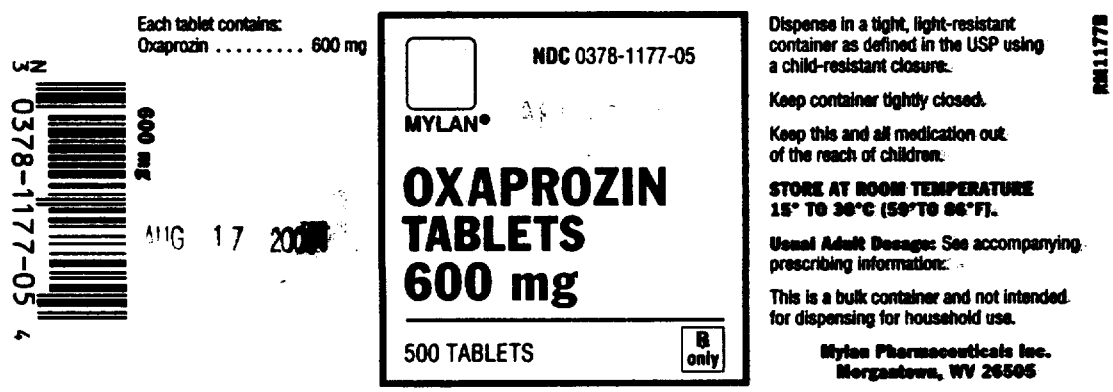
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-851

APPROVED DRAFT LABELING


NDC 0378-1177-01
MYLAN
OXAPROZIN
TABLETS
600 mg
100 TABLETS
Rx only
Each tablet contains:
Oxaprozin ..... 600 mg
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F).
Usual Adult Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM11177A
0378-1177-01
600 mg
AUG 17 2001


NDC 0378-1177-05
MYLAN
OXAPROZIN
TABLETS
600 mg
500 TABLETS
Rx only
Each tablet contains:
Oxaprozin ..... 600 mg
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT ROOM TEMPERATURE 15° TO 30°C (59°TO 86°F).
Usual Adult Dosage: See accompanying prescribing information.
This is a bulk container and not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM11177B
0378-1177-05
600 mg
AUG 17 2001

OXAP:R1

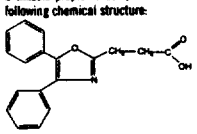
AUG 17 2001

APPROVED

OXAPROZIN TABLETS 600 mg

Rx only

DESCRIPTION: Oxaprozin is a nonsteroidal anti-inflammatory drug (NSAID), chemically designated as 4,5-diphenyl-2-oxazole-propionic acid, and has the following chemical structure:



The empirical formula for oxaprozin is $C_{18}H_{15}NO_3$, and the molecular weight is 293. Oxaprozin is a white to off-white powder with a slight odor and a melting point of 162°C to 163°C. It is slightly soluble in alcohol and insoluble in water, with an octanol/water partition coefficient of 4.8 at physiologic pH (7.4). The pK_a in water is 4.3.

Oxaprozin tablets, for oral administration, contain 600 mg of oxaprozin. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, sodium lauryl sulfate, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY: Oxaprozin is a nonsteroidal anti-inflammatory drug (NSAID) that has been shown to have anti-inflammatory, analgesic, and antipyretic properties in animal models. As with other nonsteroidal anti-inflammatory agents, all of the modes of action of oxaprozin are not fully established. Oxaprozin is an inhibitor of several steps along the arachidonic acid pathway of prostaglandin synthesis, and one of its modes of action is presumed to be due to the inhibition of prostaglandin synthesis at the site of inflammation.

Pharmacodynamics: Acute analgesic effects are demonstrable in humans after a single 1200 mg dose of oxaprozin, but anti-inflammatory effects are not reliably achieved after a single dose. Because of the long half-life of oxaprozin, it takes several days of dosing to reach steady state (see Pharmacokinetics).

Pharmacokinetics: The pharmacokinetics of oxaprozin have been evaluated in approximately 400 individuals, which have included patients with rheumatoid arthritis, osteoarthritis, healthy elderly volunteers, and patients with cardiac, renal, and hepatic disease.

Oxaprozin demonstrates high oral bioavailability (95%), with peak plasma concentrations occurring between 3 and 5 hours after dosing. Food may reduce the rate of absorption of oxaprozin, but the extent of absorption is unchanged. Antacids have no effect on the rate or extent of oxaprozin absorption.

As is true for most NSAIDs, approximately 99.9% of the oxaprozin present in plasma is bound to albumin. The fraction of the drug present in the tissues across the therapeutic dosage range ranges between 40% and 60%

s a nonsteroidal anti-inflammatory drug (NSAID) that has been shown to have anti-inflammatory, analgesic, and antipyretic properties in animal models. As with other nonsteroidal anti-inflammatory agents, all of the modes of action of oxaprozin are not fully established. Oxaprozin is an inhibitor of several steps along the arachidonic acid pathway of prostaglandin synthesis, and one of its modes of action is presumed to be due to the inhibition of prostaglandin synthesis at the site of inflammation.

Pharmacodynamics: Acute analgesic effects are demonstrable in humans after a single 1200 mg dose of oxaprozin, but anti-inflammatory effects are not reliably achieved after a single dose. Because of the long half-life of oxaprozin, it takes several days of dosing to reach steady state (see Pharmacokinetics).

Pharmacokinetics: The pharmacokinetics of oxaprozin have been evaluated in approximately 400 individuals, which have included patients with rheumatoid arthritis, osteoarthritis, healthy elderly volunteers, and patients with cardiac, renal, and hepatic disease.

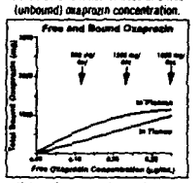
Oxaprozin demonstrates high oral bioavailability (95%), with peak plasma concentrations occurring between 3 and 5 hours after dosing. Food may reduce the rate of absorption of oxaprozin, but the extent of absorption is unchanged. Antacids have no effect on the rate or extent of oxaprozin absorption.

As is true for most NSAIDs, approximately 99.9% of the oxaprozin present in plasma is bound to albumin. The fraction of the drug present in the tissues across the therapeutic dosage range ranges between 40% and 60% of the total drug in the body and is proportional to dose, since the tissue sites are not saturated with the usual clinical doses.

Figure 1 shows the amount of oxaprozin in the plasma and in the tissue as a function of dose and the concentration of the free drug.

Figure 1.

Amount of oxaprozin in plasma and tissue as a function of dose and free (unbound) oxaprozin concentration.



Unbound oxaprozin is the pharmacologically active component; it is able to distribute into tissues and to be cleared from the body. The average unbound concentration is a function of the tissue-bound and plasma-bound drug, and it increases proportionally with dose.

As the amount of oxaprozin in the tissues increases at higher dose, the plasma concentration of oxaprozin is limited by saturation of plasma protein binding. In addition, the increase in free (unbound) oxaprozin results in an increase in clearance. Both of these contribute to the total plasma concentration of oxaprozin increasing less than proportionately with dose.

Oxaprozin kinetics were modeled using a two-compartment model with first-order absorption and protein binding that becomes saturable in the clinical dosage range. As the dose is increased from 600 to 1200 mg daily, the steady state clearance of total oxaprozin increases from 0.25 to 0.34 L/hr, the steady state apparent volume of distribution increases from 10 to 12.5 L, and the accumulation half-life decreases from 25 to 21 hours. The terminal elimination half-life is approximately twice as long as the accumulation half-life because of the increased binding and decreased clearance at lower concentrations. Steady state concentrations in clinical usage are achieved in 4 to 7 days.

Plasma levels of total oxaprozin (free and bound drug) in studies of patients taking 600 to 1200 mg/day for several months ranged from 98 to 230 mcg/mL, corresponding to estimated levels of free drug ranging from about 0.10 to 0.40 mcg/mL.

Oxaprozin is primarily metabolized in the liver, by both microsomal oxidation (65%) and glucuronic acid conjugation (35%). A small amount (< 5%) of active phenolic metabolites is produced, but the contribution to overall activity is minimal. All conjugated metabolites are inactive.

Biliary excretion of unchanged oxaprozin is a minor elimination pathway, and enterohepatic recycling of oxaprozin is insignificant. The glucuronide metabolites can be recovered from the urine (65%) and feces (35%), while unchanged oxaprozin is poorly excreted.

Renal dysfunction appears to alter oxaprozin binding and to reduce unbound clearance and unbound volume of distribution; dosage reductions should be made (see PRECAUTIONS:

[illegible] clearance at lower concentrations. Steady state concentrations in clinical usage are achieved in 4 to 7 days.

Plasma levels of total oxaprozin (free and bound drug) in studies of patients taking 600 to 1200 mg/day for several months ranged from 98 to 230 mcg/mL, corresponding to estimated levels of free drug ranging from about 0.10 to 0.40 mcg/mL.

Oxaprozin is primarily metabolized in the liver, by both microsomal oxidation (65%) and glucuronic acid conjugation (35%). A small amount (< 5%) of active phenolic metabolites is produced, but the contribution to overall activity is minimal. All conjugated metabolites are inactive.

Biliary excretion of unchanged oxaprozin is a minor elimination pathway, and enterohepatic recycling of oxaprozin is insignificant. The glucuronide metabolites can be recovered from the urine (65%) and feces (35%), while unchanged oxaprozin is poorly excreted.

Renal dysfunction appears to alter oxaprozin binding and to reduce unbound clearance and unbound volume of distribution; dosage reductions should be made (see PRECAUTIONS: General).

Age, gender, and well-compensated cardiac failure do not affect the plasma protein binding or the pharmacokinetics of oxaprozin.

Like other NSAIDs exhibiting a high degree of protein binding and a primarily metabolic route of elimination, oxaprozin has the potential for drug-drug interactions (see PRECAUTIONS: Drug Interactions).

CLINICAL STUDIES: Rheumatoid Arthritis: Oxaprozin was evaluated for managing the signs and symptoms of rheumatoid arthritis in placebo and active controlled clinical trials in a total of 646 patients. Oxaprozin was given in single or divided daily doses of 600 to 1800 mg/day and was found to be comparable to 2600 to 3900 mg/day of aspirin. At these doses there was a trend (over all trials) for oxaprozin to be more effective and cause fewer gastrointestinal side effects than aspirin.

Oxaprozin was given as a once-a-day dose of 1200 mg in most of the clinical trials, but larger doses (up to 26 mg/kg or 1800 mg/d≤y) were used in selected patients. In some patients, oxaprozin may be better tolerated in divided doses. Due to its long half-life, several days of oxaprozin therapy were needed for the drug to reach its full effect (see INDIVIDUALIZATION OF DOSAGE).

Osteoarthritis: Oxaprozin was evaluated for the management of the signs and symptoms of osteoarthritis in a total of 616 patients in active controlled clinical trials against aspirin (N = 464), piroxicam (N = 102), and other NSAIDs. Oxaprozin was given both in variable (600 to 1200 mg/day) and in fixed (1200 mg/day) dosing schedules in either single or divided doses. In these trials, oxaprozin was found to be comparable to 2600 to 3200 mg/day doses of aspirin or 20 mg/day doses of piroxicam. Oxaprozin was effective both in once-daily and in divided dosing schedules. In controlled clinical trials several days of oxaprozin therapy were needed for the drug to reach its full effects (see INDIVIDUALIZATION OF DOSAGE).

INDIVIDUALIZATION OF DOSAGE: Oxaprozin, like other NSAIDs, shows considerable interindividual differences in both pharmacokinetics and clinical response (pharmacodynamics). Therefore, the dosage for each patient should be individualized according to the patient's response to therapy.

The usual starting dose for most normal weight patients with rheumatoid arthritis is 1200 mg, once a day.

The usual starting dose for normal weight patients with mild to moderate osteoarthritis is 600 mg, once a day.

In cases where a quick onset of action is important, the pharmacokinetics of oxaprozin allow therapy to be started with a one-time loading dose of 1200 to 1800 mg (not to exceed 26 mg/kg).

Doses larger than 1200 mg/day should be reserved for patients who weigh more than 50 kg, have normal renal and hepatic function, are at low risk of peptic ulcer, and whose severity of disease justifies maximal therapy. Physicians should ensure that patients are tolerating doses in the 600 to 1200 mg/day range without gastroenterologic, renal, hepatic, or dermatologic adverse effects before advancing to the larger doses.

The maximum recommended total daily dosage is 1800 mg in divided doses.

Most patients will tolerate once-a-day dosing with oxaprozin, although divided doses may be tried in patients unable to tolerate single doses. As with all drugs of this class, the frequency and severity of adverse events will depend on the dose of the drug, the age and physical condition of the patient, any concurrent medical diagnoses, individual vulnerability, and the duration of therapy. In clinical trials of oxaprozin, no clear dose-re[illegible]

20 mg/day doses of piroxicam. Oxaprozin was effective both in once-daily and in divided dosing schedules. In controlled clinical trials several days of oxaprozin therapy were needed for the drug to reach its full effects (see INDIVIDUALIZATION OF DOSAGE).

INDIVIDUALIZATION OF DOSAGE: Oxaprozin, like other NSAIDs, shows considerable interindividual differences in both pharmacokinetics and clinical response (pharmacodynamics). Therefore, the dosage for each patient should be individualized according to the patient's response to therapy.

The usual starting dose for most normal weight patients with rheumatoid arthritis is 1200 mg, once a day.

The usual starting dose for normal weight patients with mild to moderate osteoarthritis is 600 mg, once a day.

In cases where a quick onset of action is important, the pharmacokinetics of oxaprozin allow therapy to be started with a one-time loading dose of 1200 to 1800 mg (not to exceed 26 mg/kg).

Doses larger than 1200 mg/day should be reserved for patients who weigh more than 50 kg, have normal renal and hepatic function, are at low risk of peptic ulcer, and whose severity of disease justifies maximal therapy. Physicians should ensure that patients are tolerating doses in the 600 to 1200 mg/day range without gastroenterologic, renal, hepatic, or dermatologic adverse effects before advancing to the larger doses.

The maximum recommended total daily dosage is 1800 mg in divided doses.

Most patients will tolerate once-a-day dosing with oxaprozin, although divided doses may be tried in patients unable to tolerate single doses. As with all drugs of this class, the frequency and severity of adverse events will depend on the dose of the drug, the age and physical condition of the patient, any concurrent medical diagnoses, individual vulnerability, and the duration of therapy. In clinical trials of oxaprozin, no clear dose-response relationship was seen for serious adverse effects, but physicians are cautioned that the reported safety data were developed in patients who had successfully taken lower doses of oxaprozin before being advanced above 1200 mg/day.

Experience with other NSAIDs has shown that starting therapy with maximal doses in patients at increased risk due to renal or hepatic disease, low body weight, advanced age, a known ulcer diathesis, or known sensitivity to NSAID effects is likely to increase the frequency of adverse events and is not recommended (see PRECAUTIONS).

INDICATIONS AND USAGE: Oxaprozin tablets are indicated for acute and long-term use in the management of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS: Oxaprozin tablets should not be used in patients with previously demonstrated hypersensitivity to oxaprozin tablets or any of its components or in individuals with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

Severe and occasionally fatal asthmatic and anaphylactic reactions have been reported in patients receiving NSAIDs, and there have been rare reports of anaphylaxis in patients taking oxaprozin tablets.

WARNINGS: RISK OF GASTROINTESTINAL (GI) ULCERATION, BLEEDING, AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUG THERAPY: Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Although minor upper gastrointestinal problems, such as dyspepsia, are common, and usually develop 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 for several months to 2 years, 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 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Patients at risk for developing peptic ulceration and bleeding are those with a prior history of serious GI events, alcoholism, smoking, or other factors known to be associated with peptic ulcer disease. 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 these populations. Studies to date are inconclusive concerning the relative risk of various nonsteroidal anti-inflammatory drugs

[illegible] events
alcoholism, smoking, or other factors known to be associated with peptic ulcer disease. 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 these populations. Studies to date are inconclusive concerning the relative risk of various nonsteroidal anti-inflammatory drugs (NSAIDs) in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, and substantial benefit should be anticipated to patients prior to prescribing maximal doses of oxaprozin.

PRECAUTIONS: General: ***Hepatic Effects:*** 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, remain essentially unchanged, or resolve 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 SGOT (AST) occurred in controlled clinical trials of oxaprozin in just under 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 this drug. Severe hepatic reactions including jaundice have been reported with oxaprozin, and there may be a risk of fatal hepatitis with oxaprozin, such as has been seen with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, clinical signs and symptoms consistent with liver disease develop, or systemic manifestations occur (eosinophilia, rash, fever), oxaprozin should be discontinued.

Well-compensated hepatic cirrhosis does not appear to alter the disposition of unbound oxaprozin, so dosage adjustment is not necessary. However, the primary route of elimination of oxaprozin is hepatic metabolism, so caution should be observed in patients with severe hepatic dysfunction.

Renal Effects: Acute interstitial nephritis, hematuria, and proteinuria have been reported with oxaprozin as with other NSAIDs. Long-term administration of some nonsteroidal anti-inflammatory drugs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. This was not observed with oxaprozin, but the clinical significance of this difference is unknown.

A second form of renal toxicity has been seen in patients with preexisting conditions leading to a reduction in renal blood flow, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with previously impaired renal function, heart failure, or liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is often followed by recovery to the pretreatment state. Those patients at high risk who chronically take oxaprozin should have renal function monitored if they have signs or symptoms that may be consistent with mild azotemia, such as malaise, fatigue, or loss of appetite. As with all NSAID therapy, patients may occasionally

develop some elevation of serum creatinine and BUN levels without any signs or symptoms.

The pharmacokinetics of oxaprozin may be significantly altered in patients with renal insufficiency or in patients who are undergoing hemodialysis. Such patients should be started on doses of 600 mg/day, with cautious dosage increases if the desired effect is not obtained. Oxaprozin is not dialyzed because of its high degree of protein binding.

Like other NSAIDs, oxaprozin may worsen fluid retention by the kidneys in patients with uncompensated cardiac failure due to its effect on prostaglandins. It should be used with caution in patients with a history of hypertension, cardiac decompensation, in patients on chronic diuretic therapy, or in those with other conditions predisposing to fluid retention.

Photosensitivity: Oxaprozin has been associated with rash and/or mild photosensitivity in dermatologic testing. An increased incidence of rash on sun-exposed skin was seen in some patients in the clinical trials.

Recommended Laboratory Testing: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS).

Anemia may occur in patients receiving oxaprozin or other NSAIDs. This may be due to fluid retention, gastrointestinal blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with oxaprozin should have their hemoglobin or hematocrit values determined at appropriate intervals as determined by the clinical situation.

Oxaprozin, like other NSAIDs, can affect platelet aggregation and prolong bleeding time. Oxaprozin should be used with caution in patients with underlying hemostatic defects or in those who are undergoing surgical procedures where a high degree of hemostasis is needed.

Information for Patients: Oxaprozin, like other drugs of its class, nonsteroidal anti-inflammatory drugs (NSAIDs), is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis, but they may also be commonly employed for conditions that are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of oxaprozin treatment, particularly in less-serious conditions where treatment without oxaprozin may represent an acceptable alternative to both the patient and the physician.

Patients receiving oxaprozin may benefit from physician instruction in the symptoms of the more common or serious gastrointestinal, renal, hepatic, hematologic, and dermatologic adverse effects.

Laboratory Test Interactions: False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking oxaprozin. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of oxaprozin therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish oxaprozin from benzodiazepines.

Drug Interactions: ***Aspirin:*** Concomitant administration of oxaprozin and aspirin is not recommended because oxaprozin displaces salicylates from plasma protein binding sites. Coadministration would be expected to increase the risk of salicylate toxicity.

Oral Anticoagulants: The anticoagulant effects of warfarin were not affected by the coadministration of 1200 mg/day of oxaprozin. Nevertheless, caution should be exercised when adding any drug that affects platelet function to the regimen of patients receiving oral anticoagulants.

H_2-Receptor Antagonists: The total body clearance of oxaprozin was reduced by 20% in subjects who concurrently received therapeutic doses of cimetidine or ranitidine; no other pharmacokinetic parameter was affected. A change of clearance of this magnitude lies within the range of normal variation and is unlikely to produce a clinically detectable difference in the outcome of therapy.

Beta-blockers: Subjects receiving 1200 mg oxaprozin qd with 100 mg metoprolol bid exhibited statistically significant but transient increases in sitting and standing blood pressures after 14 days. Therefore, as with all NSAIDs, routine blood pressure moni-

administration would be expected to increase the risk of salicylate toxicity.

Oral Anticoagulants: The anticoagulant effects of warfarin were not affected by the coadministration of 1200 mg/day of oxaprozin. Nevertheless, caution should be exercised when adding any drug that affects platelet function to the regimen of patients receiving oral anticoagulants.

H_2-Receptor Antagonists: The total body clearance of oxaprozin was reduced by 20% in subjects who concurrently received therapeutic doses of cimetidine or ranitidine; no other pharmacokinetic parameter was affected. A change of clearance of this magnitude lies within the range of normal variation and is unlikely to produce a clinically detectable difference in the outcome of therapy.

Beta-blockers: Subjects receiving 1200 mg oxaprozin qd with 100 mg metoprolol bid exhibited statistically significant but transient increases in sitting and standing blood pressures after 14 days. Therefore, as with all NSAIDs, routine blood pressure monitoring should be considered in these patients when starting oxaprozin therapy.

Other Drugs: The coadministration of oxaprozin and antacids, acetaminophen, or conjugated estrogens resulted in no statistically significant changes in pharmacokinetic parameters in single-and/or multiple-dose studies. The interaction of oxaprozin with lithium and cardiac glycosides has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In oncogenicity studies, oxaprozin administration for 2 years was associated with the exacerbation of liver neoplasms (hepatic adenomas and carcinomas) in male CD mice, but not in female CD mice or rats. The significance of this species-specific finding to man is unknown.

Oxaprozin did not display mutagenic potential. Results from the Ames test, forward mutation in yeast and Chinese hamster ovary (CHO) cells, DNA repair testing in CHO cells, micronucleus testing in mouse bone marrow, chromosomal aberration testing in human lymphocytes, and cell transformation testing in mouse fibroblast all showed no evidence of genetic toxicity or cell-transforming ability.

Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200 mg/kg/day (1180 mg/m^2); the usual human dose is 17 mg/kg/day (629 mg/m^2). However, testicular degeneration was observed in beagle dogs treated with 37.5 to 150 mg/kg/day (750 to 3000 mg/m^2) of oxaprozin for 6 months, or 37.5 mg/kg/day for 42 days, a finding not confirmed in other species. The clinical relevance of this finding is not known.

Pregnancy: *Teratogenic Effects.*

Pregnancy Category C: There are no adequate or well-controlled studies in pregnant women. Teratology studies with oxaprozin were performed in mice, rats, and rabbits. In mice and rats, no drug-related developmental abnormalities were observed at 50 to 200 mg/kg/day of oxaprozin (225 to 900 mg/m^2). However, in rabbits, infrequent malformed fetuses were observed in dams treated with 7.5 to 30 mg/kg/day of oxaprozin (the usual human dosage range). Oxaprozin should be used durieg pregnancy only if the potential benefits justify the potential risks to the fetus.

Labor and Delivery: The effect of oxaprozin in pregnant women is unknown. NSAIDs are known to delay parturition, to accelerate closure of the fetal ductus arteriosus, and to be associated with dystocia. Oxaprozin is known to have caused decreases in pup survival in rat studies. Accordingly, the use of oxaprozin during late pregnancy should be avoided.

Nursing Mothers: Studies of oxaprozin excretion in human milk have not been conducted; however, oxaprozin was found in the milk of lactating rats. Since the effects of oxaprozin on infants are not known, caution should be exercised if oxaprozin is administered to nursing women.

Pediatric Use: Safety and effectiveness of oxaprozin in pediatric patients have not been established.

Geriatric Use: No adjustment of the dose of oxaprozin is necessary in the elderly for *pharmacokinetic* reasons, although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging. No significant differences in the pharmacokinetic profile for oxaprozin were seen in studies in the healthy elderly.

Although selected elderly patients in controlled clinical trials tolerated oxaprozin as well as younger patients, caution should be exercised in treating the elderly, and extra care should be taken when choosing a dose. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

ADVERSE REACTIONS: Adverse reac-

pup survival in rat studies. Accordingly, the use of oxaprozin during late pregnancy should be avoided.

Nursing Mothers: Studies of oxaprozin excretion in human milk have not been conducted; however, oxaprozin was found in the milk of lactating rats. Since the effects of oxaprozin on infants are not known, caution should be exercised if oxaprozin is administered to nursing women.

Pediatric Use: Safety and effectiveness of oxaprozin in pediatric patients have not been established.

Geriatric Use: No adjustment of the dose of oxaprozin is necessary in the elderly for *pharmacokinetic* reasons, although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging. No significant differences in the pharmacokinetic profile for oxaprozin were seen in studies in the healthy elderly.

Although selected elderly patients in controlled clinical trials tolerated oxaprozin as well as younger patients, caution should be exercised in treating the elderly, and extra care should be taken when choosing a dose. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

ADVERSE REACTIONS: Adverse reaction data were derived from patients who received oxaprozin in multidose, controlled, and open-label clinical trials, and from worldwide marketing experience. Rates for events occurring in more than 1% of patients, and for most of the less common events, are based on 2253 patients who took 1200 to 1800 mg oxaprozin per day in clinical trials. Of these, 172% were treated for at least 1 month, 971 for at least 3 months, and 366 for more than 1 year. Rates for the rarer events and for events reported from worldwide marketing experience are difficult to estimate accurately and are only listed as less than 1%.

The adverse event rates below refer to the incidence in the first month of use. Most of the events were seen by this time for common adverse reactions. However, the cumulative incidence can be expected to rise with continued therapy, and some events, such as gastrointestinal bleeding (see WARNINGS), seem to occur at a constant or possibly increasing rate over time.

The most frequently reported adverse reactions were related to the gastrointestinal tract. They were nausea (8%) and dyspepsia (8%).

Incidence Greater Than 1%: In clinical trials the following adverse reactions occurred at an incidence greater than 1% and are probably related to treatment. Reactions occurring in 3% to 9% of patients treated with oxaprozin are indicated by an asterisk (*); those reactions occurring in less than 3% of patients are unmarked.

Digestive System: abdominal pain/distress, anorexia, constipation*, diarrhea*, dyspepsia*, flatulence, nausea*, vomiting.

Nervous System: CNS inhibition (depression, sedation, somnolence, or confusion), disturbance of sleep.

Skin and Appendages: rash*.

Special Senses: tinnitus.

Urogenital System: dysuria or frequency.

Incidence Less Than 1%: ***Probable Causal Relationship:*** The following adverse reactions were reported in clinical trials or from worldwide marketing experience at an incidence of less than 1%. Those reactions reported only from worldwide marketing experience are in *italics*. The probability of a causal relationship exists between the drug and these adverse reactions.

Body as a Whole: drug hypersensitivity reactions including anaphylaxis *and serum sickness.*

Cardiovascular System: edema, blood pressure changes.

Digestive System: peptic ulceration and/or GI bleeding (see WARNINGS), liver function abnormalities including *hepatitis* (see PRECAUTIONS), stomatitis, hemorrhoidal or rectal bleeding, *pancreatitis.*

Hematologic System: anemia, thrombocytopenia, leukopenia, ecchymoses, *agranulocytosis, pancytopenia.*

Metabolic System: weight gain, weight loss.

Nervous System: weakness, malaise.

Respiratory System: symptoms of upper respiratory tract infection.

Skin: pruritus, urticaria, photosensitivity, *pseudoporphyria, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).*

Special Senses: blurred vision, conjunctivitis.

Urogenital: acute interstitial nephritis, nephrotic syndrome, hematuria, renal insufficiency, *acute renal failure,* decreased menstrual flow.

Causal Relationship Unknown: The following adverse reactions occurred at an incidence of less than 1% in clinical trials, or were suggested from marketing experience, under circum-

incidence greater than 1% in clinical trials, the following adverse reactions occurred at an incidence greater than 1% and are probably related to treatment. Reactions occurring in 3% to 9% of patients treated with oxaprozin are indicated by an asterisk (*); those reactions occurring in less than 3% of patients are unmarked.

Digestive System: abdominal pain/distress, anorexia, constipation*, diarrhea*, dyspepsia*, flatulence, nausea*, vomiting.

Nervous System: CNS inhibition (depression, sedation, somnolence, or confusion), disturbance of sleep.

Skin and Appendages: rash*.

Special Senses: tinnitus.

Urogenital System: dysuria or frequency.

Incidence Less Than 1%: ***Probable Causal Relationship:*** The following adverse reactions were reported in clinical trials or from worldwide marketing experience at an incidence of less than 1%. Those reactions reported only from worldwide marketing experience are in *italics*. The probability of a causal relationship exists between the drug and these adverse reactions.

Body as a Whole: drug hypersensitivity reactions including anaphylaxis *and serum sickness.*

Cardiovascular System: edema, blood pressure changes.

Digestive System: peptic ulceration and/or GI bleeding (see WARNINGS), liver function abnormalities including *hepatitis* (see PRECAUTIONS), stomatitis, hemorrhoidal or rectal bleeding, *pancreatitis.*

Hematologic System: anemia, thrombocytopenia, leukopenia, ecchymoses, *agranulocytosis, pancytopenia.*

Metabolic System: weight gain, weight loss.

Nervous System: weakness, malaise.

Respiratory System: symptoms of upper respiratory tract infection.

Skin: pruritus, urticaria, photosensitivity, *pseudoporphyria, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).*

Special Senses: blurred vision, conjunctivitis.

Urogenital: acute interstitial nephritis, nephrotic syndrome, hematuria, renal insufficiency, *acute renal failure,* decreased menstrual flow.

Causal Relationship Unknown: The following adverse reactions occurred at an incidence of less than 1% in clinical trials, or were suggested from marketing experience, under circumstances where a causal relationship could not be definitely established. They are listed as alerting information for the physician.

Cardiovascular System: palpitations.

Digestive System: alteration in taste.

Respiratory System: sinusitis, pulmonary infections.

Skin and Appendages: alopecia.

Special Senses: hearing decrease.

Urogenital System: increase in menstrual flow.

DRUG ABUSE AND DEPENDENCE: Oxaprozin is a non-narcotic drug. Usually reliable animal studies have indicated that oxaprozin has no known addiction potential in humans.

OVERDOSAGE: No patient experienced either an accidental or intentional overdosage of oxaprozin in the clinical trials of the drug. Symptoms following acute overdose with other NSAIDs are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain and are generally reversible with supportive care. Gastrointestinal bleeding and coma have occurred following NSAID overdose. Hypertension, acute renal failure, and respiratory depression are rare.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, alkalization of the urine, or hemoperfusion would probably not be useful due to the high degree of protein binding of oxaprozin.

DOSAGE AND ADMINISTRATION: Rheumatoid Arthritis: The usual daily dose of oxaprozin tablets in the management of the signs and symptoms of rheumatoid arthritis is 1200 mg (two 600 mg tablets) once a day. Both smaller and larger doses may be required in individual patients (see INDIVIDUALIZATION OF DOSAGE).

Osteoarthritis: The usual daily dose of oxaprozin tablets for the management of the signs and symptoms of moderate to severe osteoarthritis is 1200 mg (two 600 mg tablets) once a day. For patients of low body weight or with milder disease, an initial dosage of one 600 mg tablet once a day may be appropriate (see INDIVIDUALIZATION OF DOSAGE).

Regardless of the indication, the dosage should be individualized to the lowest effective dose of oxaprozin

Forced diuresis, dialysis, alkalinization of the urine, or hemoperfusion would probably not be useful due to the high degree of protein binding of oxaprozin.

DOSAGE AND ADMINISTRATION: Rheumatoid Arthritis: The usual daily dose of oxaprozin tablets in the management of the signs and symptoms of rheumatoid arthritis is 1200 mg (two 600 mg tablets) once a day. Both smaller and larger doses may be required in individual patients (see INDIVIDUALIZATION OF DOSAGE).

Osteoarthritis: The usual daily dose of oxaprozin tablets for the management of the signs and symptoms of moderate to severe osteoarthritis is 1200 mg (two 600 mg tablets) once a day. For patients of low body weight or with milder disease, an initial dosage of one 600 mg tablet once a day may be appropriate (see INDIVIDUALIZATION OF DOSAGE).

Regardless of the indication, the dosage should be individualized to the lowest effective dose of oxaprozin tablets to minimize adverse effects, and the maximum recommended total daily dose is 1800 mg (or 26 mg/kg, whichever is lower) in divided doses.

SAFETY AND HANDLING: Oxaprozin is supplied as a solid dosage form in closed containers, is not known to produce contact dermatitis, and poses no known risk to healthcare workers. It may be disposed of in accordance with applicable local regulations governing the disposal of pharmaceuticals.

HOW SUPPLIED: Oxaprozin Tablets are available containing 600 mg of oxaprozin. The tablets are white, film-coated, oval, biconvex, beveled edge tablets debossed with 11 to the left of the score and 77 to the right of the score on one side of the tablet and **MYLAN** on the other side. They are available as follows:

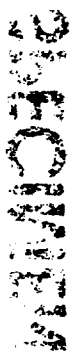
NDC 0378-1177-01
bottles of 100 tablets
NDC 0378-1177-05
bottles of 500 tablets

STORE AT ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F).
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

DECEMBER 2000
OXAP:R1



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-851

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.: 3 2. ANDA: 75-851

3. NAME AND ADDRESS OF APPLICANT:
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26504-4310
Telephone: 304-599-2595
Fax: 304-285-6407

4. LEGAL BASIS FOR SUBMISSION: Daypro® (Oxaprozin) Caplets, 600 mg manufactured by G.D. Searle & Co. There are no patents that claim the listed drug. The New Chemical Exclusivity provision expired in October 29, 1999 and the Pediatric Exclusivity expired in April 29, 2000.

5. SUPPLEMENTS: N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Oxaprozin

8. SUPPLEMENT PROVIDES FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Original Submission	April 28, 2000
Acknowledgement of Receipt (FDA)	May 22, 2000
Deficiency Letter	December 6, 2000
Major Amendment	**January 17, 2001**
Fax Amendment (FDA)	**June 22, 2001**
Fax Amendment (Response)	**July 13, 2001**
Telephone Amendment (FDA)	**July 19, 2001**
Telephone Amendment (Response)	**July 19, 2001**

20 Sept 2001

10. PHARMACOLOGICAL CATEGORY: For the acute and long-term use in the management of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

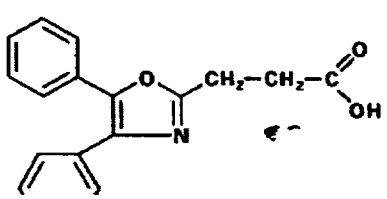
11. R_x/OTC: R

12. RELATED IND/NDA/DMF(s): See item 38.

13. DOSAGE FORM: Tablet (capsule-shaped)/Oral

14. POTENCY: 600 mg

15. CHEMICAL NAME AND STRUCTURE:



4,5-diphenyl-2-oxazolepropionic acid

16. RECORDS AND REPORTS: N/A

17. COMMENTS: N/A

18. CONCLUSIONS AND RECOMMENDATIONS: **Approvable**

19. REVIEWER: David J. Cummings DATE COMPLETED: 06-Jun-01
Revised: 07-Jun-01,
Revised 26-Jul-01

cc:

ile

Endorsements:

8/14/2001
8-14-01

Page(s) 16

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

chem Rev 3
6/7/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-851

BIOEQUIVALENCE

OXAPROZIN TABLETS
600 mg
ANDA 75-851
Reviewer: Z.Z.Wahba
V:\Firmsam\Mylan\ltrs&rev\75851a1.900

Mylan Pharmaceuticals
Morgantown, WV
Submission Date: 09/05/00
10/06/00

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm has previously submitted two in vivo bioequivalence studies (single-dose under fasting and fed conditions) comparing its test product Oxaprozin Tablet, 600 mg to the reference listed drug, Searle's Daypro® Tablet, 600 mg. The Division of Bioequivalence has reviewed the submission and the studies have been found to be incomplete due to the deficiency comment. See the review dated 8/18/2000.

2. In this submission, the firm responded to the deficiency comment and provided additional dissolution testing data.

DEFICIENCY COMMENT

The firm was asked to resubmit comparative dissolution testing data according to the Agency's specification. The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.4, at 37 °C using USP apparatus II (paddle) at 75 rpm.

RESPONSE TO THE DEFICIENCY COMMENT

The dissolution testing for the test and reference products is summarized below:

Method:	FDA method
Apparatus:	USP 24 apparatus II (paddle) at 75 rpm
Medium:	0.05 M phosphate buffer, pH 7.4
Volume:	1000 mL
Number of Units:	12 Tablets
Specifications:	NLT in 45 minutes.
Test products:	Mylan's Oxaprozin Tablets 600 mg, lot #2C012A (expired Bio-lot, manufactured on 1/26/98), and lot #R1G2776 (current batch, manufactured on 4/25/2000).
Reference products:	Searle's Daypro® tablets, 600 mg, lot#5K924 (expired Bio-lot, expiration date: 2/98), and lot #0K793 (current batch, expiration date 2/2003).

Results: Copies of the dissolution data statements are included in this report (Attachments #1-4).

Conclusion: The dissolution data for the test and reference products are acceptable.

The firm's response to the deficiency comment is acceptable.

RECOMMENDATIONS

1. The two in vivo bioequivalence studies, single-dose under fasting (study #OXAP-9590) and non-fasting (study #OXAP-9595) conditions, conducted by Mylan Pharmaceuticals on its Oxaprozin Tablet, 600 mg, comparing it to the reference listed drug Searle's Daypro® Tablet, 600 mg, have been found to be acceptable to the Division of Bioequivalence. The two studies demonstrate that under fasting and non-fasting conditions, Mylan's Oxaprozin Tablet, 600 mg is bioequivalent to Searle's Daypro® Tablet, 600 mg.

2. The dissolution testing conducted by the firm on its Oxaprozin Tablet, 600 mg has been found acceptable.

3. 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 0.05 M phosphate buffer, pH 7.4, at 37°C using USP apparatus II (Paddle) at 75 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Zakaria Z Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

for RD INITIALLED BDAVIT
FT INITIALLED BDAVIT

Concur: Barbara M Davit Date: 10/25/00

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Attachment #1
ANDA# 75-851

DISSOLUTION PROFILE

PRODUCT: Oxaprozin Tablets
LOT NO.: 2C012A
DOSAGE: 600 mg DATE OF ASSAY: 08/30/00

CONDITION:

Dissolution Medium: 0.05 M Potassium Phosphate Buffer, pH 7.4 ± 0.05, 1000 mL @ 37°C ± 0.5°C
Apparatus: 2 (paddle) @ 75 rpm
Sample Times: 10, 20, 30 and 45 minutes

	Time 10 min.	Time 20 min.	Time 30 min.	Time 45 min.
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
MEAN	89%	96%	98%	99%
RANGE	86%-97%	94%-107%	95%-109%	96%-110%
SD	2.9	3.6	3.7	3.7
RSD	3.3%	3.7%	3.8%	3.8%

PREPARED BY _____ DATE 9.5.00

APPROVED BY _____ DATE 09/05/00

G:RDLAB\DISSOLUTION\Oxaprozin 2C012A

Attachment #2

DISSOLUTION PROFILE

PRODUCT: Daypro®Tablets EXP. DATE: 02/98
LOT NO.: 5K924
DOSAGE: 600 mg DATE OF ASSAY: 08/30/00

CONDITION:

Dissolution Medium: 0.05 M Potassium Phosphate Buffer, pH 7.4 ± 0.05, 1000 mL @ 37°C ± 0.5°C
Apparatus: 2 (paddle) @ 75 rpm
Sample Times: 10, 20, 30 and 45 minutes

	Time 10 min.	Time 20 min.	Time 30 min.	Time 45 min.
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
MEAN	88%	99%	100%	101%
RANGE	82%-91%	97%-100%	98%-101%	99%-102%
SD	3.3	1.0	1.0	0.9
RSD	3.7%	1.0%	1.0%	0.9%

PREPARED BY _____ DATE 8.31.00

APPROVED BY _____ DATE 08/31/00

G:\RDLAB\DISSOLUTION\Daypro 5K924

Attachment #3

DISSOLUTION PROFILE

PRODUCT: Oxaprozin Tablets
LOT NO.: R1G2776
DOSAGE: 600 mg **DATE OF ASSAY:** 08/30/00

CONDITION:

Dissolution Medium: 0.05 M Potassium Phosphate Buffer, pH 7.4 ± 0.05, 1000 mL @ 37°C ± 0.5°C
Apparatus: 2 (paddle) @ 75 rpm
Sample Times: 10, 20, 30 and 45 minutes

	Time 10 min.	Time 20 min.	Time 30 min.	Time 45 min.
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
MEAN	95%	99%	99%	99%
RANGE	92%-98%	97%-100%	98%-100%	98%-100%
SD	1.5	1.0	0.8	0.7
RSD	1.6%	1.0%	0.8%	0.7%

PREPARED BY _____ DATE 8-31-00

APPROVED BY _____ DATE 08/31/00

G:\RDLAB\DISSOLUTION\Oxaprozin

Attachment #4

DISSOLUTION PROFILE

PRODUCT: Daypro®Tablets EXP. DATE: 02/03
LOT NO.: 0K793
DOSAGE: 600 mg DATE OF ASSAY: 08/30/00

CONDITION:

Dissolution Medium: 0.05 M Potassium Phosphate Buffer, pH 7.4 ± 0.05, 1000 mL @ 37°C ± 0.5°C
Apparatus: 2 (paddle) @ 75 rpm
Sample Times: 10, 20, 30 and 45 minutes

	Time 10 min.	Time 20 min.	Time 30 min.	Time 45 min.
1.				
2.				%
3.				9%
4.				00%
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
MEAN	56%	91%	98%	100%
RANGE	51%-61%	87%-94%	97%-100%	99%-101%
SD	2.9	2.1	0.8	0.6
RSD	5.2%	2.4%	0.8%	0.6%

PREPARED BY ABowen DATE 10/3/00

APPROVED BY Jlehmann DATE 10·3·00

G:RDLAB\DISSOLUTION\Daypro 0K793

OXAPROZIN TABLETS
600 mg
ANDA 75-851
Reviewer: Z.Z.Wahba
V:\Firmsam\Mylan\ltrs&rev\75851sd.400

Mylan Pharmaceuticals
Morgantown, WV
Submission Date: 04/28/00

Review of Bioequivalence Studies, and Dissolution Data (Electronic Submission)

Introduction

Indication: The drug is used for management of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Type of Submission: Original

Contents of Submission: Two in vivo bioequivalence studies under fasting and non-fasting conditions and dissolution data.

RLD: Searle's Daypro® tablets, 600 mg, marketed by G.D. Searle & Co.

Recommended Dose: The usual daily dose of Daypro® for patients with rheumatoid arthritis is 1200 mg (two 600 mg caplets) and for patients with osteoarthritis an initial dosage of 600 mg caplet once a day may be appropriate. The maximum recommended total daily dose is 1800 mg in divided doses.

Background

Oxaprozin is a nonsteroidal anti-inflammatory drug, chemically designated as 4,5-diphenyl-2-oxazole-propionic acid.

The mechanism of actions of oxaprozin is not fully established. Oxaprozin is an inhibitor of several steps along the arachidonic acid pathway of prostaglandin synthesis, and one of its modes of action is presumed to be due to inhibition of prostaglandin synthesis at the site of inflammation.

The bioavailability of oxaprozin is about 95%, with peak plasma concentrations occurring between 3 and 5 hours after dosing. Food may reduce the rate of absorption of the drug, but the extent of absorption is unchanged. Antacids have no effect on the rate or extent of oxaprozin absorption. Approximately 99.9% of oxaprozin present in the plasma is bound to albumin. The fraction of the drug present in the tissues across the therapeutic dosage ranges between 40% and 60% of the total drug in the body and is proportional to dose, since the tissue sites are not saturated with the usual

clinical doses. The half-life predictive of accumulation ranges between 25 hours (600 mg daily) and 21 hours (1200 mg daily). Steady state concentrations in clinical usage are achieved in 4 to 7 days.

Oxaprozin is primarily metabolized in the liver, by both microsomal oxidation (65%) and glucuronic acid conjugation (34%). A small amount (<5%) of active phenolic metabolites is produced, but the contribution to overall activity is minimal. All conjugated metabolites are inactive. Biliary excretion of unchanged oxaprozin is a minor elimination pathway, and enterohepatic recycling of oxaprozin is insignificant.

The Firm's Financial Disclosure:

The firm's financial disclosure statements submitted with the bioequivalence section in support of this application did not indicate any conflict of interests between the CRO's investigators and the firm.

Protocol No.: **Comparative Two-Way Single-Dose Bioavailability Study of Oxaprozin Tablets in Healthy Fasting Male Volunteers**

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	CLINICAL AND PHARMACOLOGIC RESEARCH, INC
Medical Director & Principle Investigator:	
Scientific Director:	
Clinical Study Dates:	04/13/96 to 05/19/96
Analytical Facility	MYLAN PHARMACEUTICALS INC.
Analytical Study Dates:	05/24/96 to 06/28/96

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	oxaprozin tablets	Daypro
Manufacturer:	Mylan Pharmaceuticals Inc.	G.D. Searle & Co.
Manufacture Date:	1/26/96	N/A
Expiration Date:	N/A	2/98
ANDA Batch Size:		N/A
Batch/Lot Number:	2C012A	5K924
Potency:	99.3%	98.6%
Content Uniformity:	99.5%	98.0%
Strength:	600 mg	600 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	600 mg	600 mg

Study Condition:	Fasting	Fasting	
Length of Fasting:	10 hours	10 hours	

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	21 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	33
Route of Administration:	oral	**No. of Subjects Completing:**	30
Dosing Interval:	hr	**No. of Subjects Plasma Analyzed:**	30
Number of Doses:	N/A	**No. of Dropouts:**	3
Loading Dose:	mg	**Sex(es) Included:**	male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	1

Dietary Restrictions:	No alcohol, caffeine or xanthine-containing food or beverages within 48 hours prior to the initial dose of study medication. No change in dietary or exercise habits throughout the duration of the study.
Activity Restrictions:	Subjects will engage in normal activity for the first 12 hours after drug administration, avoiding both vigorous exertion and complete rest.
Drug Restrictions:	No medications allowed during the study or washout for 14 days prior to the study. Any medication known to alter hepatic enzyme activity within 30 days prior to dosing. No vitamins within 48 hours prior to dosing.
Blood Sampling:	Serial blood samples (10 mL) were collected predose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12, 24, 48, 72, 96, 120, 192, 264 and 336 hours post-dose. Plasma was extracted and stored in labeled tubes at -20°C or lower until analysis.

Study Results

1) Clinical

Adverse Events: (pages #290, and #438, volume C1.2)

There was only one subject (subject #31) experienced symptoms of mild lightheadedness and feeling faint. All subjects completed the clinical study.

Dropouts:

SUBJECT NO.:	29	31	33
REASON:	Dropped out during Period 1 because he moved out of the area	failed to report for Period 2 due to personal reasons which were not study	Discontinued during Period 2 because he was exposed to meningitis and was

		related.	required to take medicine
PERIOD:	1	2	2
REPLACEMENT:	N	N	N

2) Analytical (Not to be Released Under FOI)
Pre-Study Assay Validation:

ANALYTE:	OXAPROZIN
ASSAY METHOD:	
MATRIX:	Plasma
INTERNAL STANDARD:	
SENSITIVITY:	0.5 ug/ml
STANDARD CURVE HIGHEST CONC.:	100 ug/ml
STANDARD CURVE LOWEST CONC.:	0.5 ug/ml
R**2 IS GREATER THAN:	0.98
SPECIFICITY:	Y
ANALYTE RETENTION TIME:	7.9-9.2 minutes
INTERNAL STANDARD RETENTION TIME:	5.3-6.0 minutes
WITHIN-DAY ACCURACY (% change)	-1.1 to 4.8%
WITHIN-DAY PRECISION (% CV)	1.3 to 2.3
BETEEN-DAY ACCURACY (% change)	-0.6 to 0.2
BETEEN-DAY PRECISION (% CV)	2.3 to 3.2
RECOVERY	85.96%
STABILITY	Long term: stable for up to 89 days Room Temp.: up to 96 hours Freeze/thaw Stability: for 3 cycles

3) Pharmacokinetic:

Note: Eight subjects (Subjects #5, #13, #18, and #28 for Treatment A and Subject #3, #11, #12 and #16 fir Treatment B) exhibited a non-zero concentration in Period 2. This carryover residual phenomenon may be due to a long half-life of oxaprozin for these subjects. The non-zero concentration for those subjects ranged from 0.7 to 2.6% of the corresponding Cmax for each subject. The carryover residual is not expected to affect on the overall outcome of the biostudy. The firm did the calculation on plasma data that were adjusted for carryover residual. In addition, the reviewer performed SAS-GLM procedure analysis on the plasma data without carryover residue adjustment and the outcome was similar the values presented by the sponsor. The statistical analyses are presented below:

Table 1

Mean (SD) Plasma Concentrations of OXAPROZIN

Treatment A = oxaprozin tablets, 600 mg tablet, Dose Administered = 600 mg, fasting

Treatment B = Daypro, 600 mg tablet, Dose Administered = 600 mg, fasting

Time(hours)	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Ratio (A)/(B)
0	0.13	295.74	0.13	293.39	0.988
0.5	13.99	109.93	18.03	77.97	0.776
1.0	36.44	47.59	48.76	40.03	0.747
1.5	45.4	32.31	56.22	36.48	0.808
2.0	51.73	27.24	59.24	28.57	0.873
2.5	55.59	24.62	63.86	20.03	0.871
3.0	57.9	19.37	63.48	17.41	0.912
3.5	56.97	17.24	60.97	13.13	0.934
4.0	56.54	15.2	61.03	13.95	0.926
5.0	56.82	15.19	61.94	14.89	0.917
6.0	52.95	14.93	57.29	15.88	0.924
8.0	49.45	14.49	52.43	14.05	0.943
12	46.15	12.83	48.16	14.83	0.958
24	43.49	12.89	42.79	14.59	1.016
48	33.13	16.71	32.34	18.03	1.024
72	24.39	21.3	23.89	25.61	1.021
96	18.59	27.82	18.09	31.09	1.028
120	14.0	35.72	13.78	39.56	1.016
192	7.0	48.25	6.5	58.73	1.076
264	3.35	73.82	3.21	71.99	1.045
336	1.71	95.45	1.58	101.36	1.084

Table 2

OXAPROZIN Pharmacokinetic Parameters

Treatment A = oxaprozin tablets, 600 mg tablet, Dose Administered = 600 mg, fasting

Treatment B = Daypro, 600 mg tablet, Dose Administered = 600 mg, fasting

Arithmetic Means

Parameter	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Ratio (A)/(B)
AUCT	4904.265	25.356	4876.705	26.166	1.006
AUCI	5149.137	27.689	5083.97	28.627	1.013
CMAX	61.43	14.792	69.063	15.248	0.889
TMAX	3.217	35.04	2.433	43.079	1.322
KEL	0.011	29.572	0.011	28.323	0.971
THALF	67.611	29.909	64.912	27.108	1.042

Geometric Means:

AUCT	4749.014	4720.128	1.006
AUCI	4969.327	4895.414	1.015
CMAX	60.765	68.286	0.89

Table 3

Summary Statistics for OXAPROZIN

Treatment A = oxaprozin tablets, 600 mg tablet, Dose Administered = 600 mg, fasting

Treatment B = Daypro, 600 mg tablet, Dose Administered = 600 mg, fasting

A vs B Arithmetic & Geometric Means (the firm calculated data)

Parameter	A	B	Ratio A/B	C.I. 90%
AUCI	4537	4500		
AUCL	4400	4387		
CPEAK	61.2	70.2		
HALF	58.4	57.1		
KEL	0.0124	0.0127		
LNAUCI	8.4	8.39	1.01	97 - 105
LNAUCL	8.37	8.37	1	96 -105
LNCPEAK	4.1	4.24	0.87	82 - 92
TPEAK	3.14	2.36		

Table 4

LSMEANS AND 90% CONFIDENCE INTERVALS (SAS output, prepared by the reviewer)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	4979.75	4911.82	1.01	98.53	104.32
LAUCT	4758.92	4736.40	1.00	97.27	103.79
LCMAX	60.84	68.39	0.89	85.05	93.07

MEAN1=Test-product MEAN2=Ref.-product
UNIT: AUC=MCG.HR/ML CMAX=MCG/ML
LOWCI 12=Lower C.I. for T/R UPPCI12=Upper C.I. for T/R

Comment on the fasting study:

Under fasting conditions, the mean plasma Oxaprozin levels for the test and reference products were comparable to each other as shown in Table #1 and Figure #1. The 90% confidence intervals for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Tables #3 &4). The T/R mean ratios (RLSM12) for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25% (Tables #3 & 4).

Protocol No.: OXAP-9595, Comparative, Three-Way Single Dose Bioavailability Study of Oxaprozin Tablets in Healthy Male Volunteers Under Post-Prandial Conditions

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	CLINICAL AND PHARMACOLOGIC RESEARCH, INC
Medical Director:	s
Scientific Director:	
Clinical Study Dates:	04/20/96 to 07/07/96
Analytical Facility	MYLAN PHARMACEUTICALS INC.
Principal Investigator:	Walt Owens
Analytical Study Dates:	06/26/96 to 07/23/96

TREATMENT INFORMATION

Treatment ID:	A	B	C
Test or Reference:	T	R	T
Product Name:	oxaprozin tablets	Daypro	oxaprozin tablets
Manufacturer:	Mylan Pharmaceuticals Inc.	G.D. Searle & Co.	Mylan Pharmaceuticals Inc.
Manufacture Date:	1/26/96	N/A	1/26/96
Expiration Date:	N/A	2/98	N/A
ANDA Batch Size:		N/A	
Batch/Lot Number:	2C012A	5K924	2C012A
Potency:	99.3%	98.6%	93.3%
Content Uniformity:	99.5%	98.0%	99.5%
Strength:	600 mg	600 mg	600 mg
Dosage Form:	tablet	Tablet	tablet
Dose Administered:	600 mg	600 mg	600 mg
Study Condition:	fed	Fed	fasting
Length of Fasting:	N/A	N/A	10 hours
Standardized Breakfast:	Y	Y	N
Breakfast Specifics:	1 buttered English muffin, 1 fried egg, 1 slice of Canadian bacon, 1 slice of American cheese, 3 ounce serving of hashed brown potatoes, 6 ounces of orange juice, and 8 ounces of whole milk	1 buttered English muffin, 1 fried egg, 1 slice of Canadian bacon, 1 slice of American cheese, 3 ounce serving of hashed brown potatoes, 6 ounces orange juice, 8 ounces whole milk	N/A

RANDOMIZATION		**DESIGN**	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	6	**Replicated Treatment Design:**	N
No. of Periods:	3	**Balanced:**	Y
No. of Treatments:	3	**Washout Period:**	21 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	23
Route of Administration:	oral	**No. of Subjects Completing:**	18
Dosing Interval:	hr	**No. of Subjects Plasma Analyzed:**	18
Number of Doses:	N/A	**No. of Dropouts:**	5
Loading Dose:	mg	**Sex(es) Included:**	Male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	0

Dietary Restrictions:	No ingestion of any alcoholic, caffeine-, or xanthine-containing food or beverage within 48 hours prior to dosing. No change in diet or exercise during the course of the study.
Activity Restrictions:	Subjects will engage in normal activity for the first 12 hours after drug administration, avoiding both vigorous exertion and complete rest.
Drug Restrictions:	No concurrent medication allowed during the study (including the washout period) or for 14 days prior to the study. No use of any medication known to alter hepatic enzyme activity within 30 days of dosing. No vitamins within 48 hours of dosing.
Blood Sampling:	Serial blood samples (10 mL) were collected predose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12, 24, 48, 72, 96, 120, 192, 264 and 336 hours post-dose. Plasma was extracted and stored in labeled tubes at -20°C or lower until analysis

Study Results

1) Clinical

Adverse Events: (page #1620, volume 1.5)

There were no adverse events reported for this study.

Dropouts:

SUBJECT NO.:	12	2	21	3
REASON:	Did not report for Period 2 due to personal reasons not study related	Did not report for Period 2 due to personal reasons not study related	Failed to report	Did not report for Period 2 due to personal reasons not study related
PERIOD:	2	2	2	2
REPLACEMENT:	N	N	N	N

SUBJECT NO.:	6
REASON:	Did not report for Period 2 due to personal reasons not study related
PERIOD:	2
REPLACEMENT:	N

2) Analytical (Not to be Released Under FOI)

The same as in the study under fasting conditions (Protocol #OXAP-9590).

3) Pharmacokinetic:

Table 5

Mean (SD) Plasma Concentrations of OXAPROZIN

Treatment A = oxaprozin tablets, 600 mg tablet, Dose Administered = 600 mg, fed

Treatment B = Daypro, 600 mg tablet, Dose Administered = 600 mg, fed

Treatment C = oxaprozin tablets, 600 mg tablet, Dose Administered = 600 mg, fasting

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.04	0.16	0.03	0.12	0.07	0.22	1.27
0.5	4.96	8.29	5.67	10.61	12.56	16.69	0.88
1	24.45	17.23	20.82	17.50	31.88	23.25	1.17
1.5	37.83	18.53	34.41	14.91	39.92	22.13	1.10
2	46.00	17.19	43.54	15.21	46.11	22.20	1.06
2.5	48.54	12.64	46.93	13.82	49.11	20.91	1.03
3	52.85	11.25	50.57	12.41	51.95	21.09	1.05
3.5	54.75	8.45	56.77	11.28	52.45	19.78	0.96
4	56.27	6.85	58.94	9.19	53.58	17.56	0.95
5	58.13	9.88	61.85	9.84	55.61	15.30	0.94
6	54.94	7.76	58.79	7.67	53.03	14.84	0.93
8	50.66	8.25	53.74	7.11	48.43	11.34	0.94
12	46.50	7.00	49.53	5.96	46.46	8.61	0.94
24	41.57	6.03	41.72	5.11	42.08	6.72	1.00
48	30.71	5.45	30.42	4.75	30.90	6.05	1.01
72	22.55	5.06	22.07	4.55	22.42	5.02	1.02
96	16.21	4.58	15.94	4.13	16.68	4.49	1.02
120	11.97	3.86	11.80	3.60	12.46	3.93	1.01
192	5.17	2.55	5.34	2.53	5.37	2.70	0.97
264	2.37	1.63	2.42	1.49	2.49	1.73	0.98
336	0.97	1.11	1.02	1.01	1.02	1.02	0.95

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0	0.51	0.40
0.5	0.40	0.45
1	0.77	0.65
1.5	0.95	0.86
2	1.00	0.94
2.5	0.99	0.96
3	1.02	0.97
3.5	1.04	1.08
4	1.05	1.10
5	1.05	1.11
6	1.04	1.11
8	1.05	1.11

12	1.00	1.07
24	0.99	0.99
48	0.99	0.98
72	1.01	0.98
96	0.97	0.96
120	0.96	0.95
192	0.96	0.99
264	0.95	0.97
336	0.96	1.00

1=Test-NonFast 2=Ref.-NonFast 3=Test-Fast
UNIT: PLASMA LEVEL=MCG/ML TIME=HRS

Table 6

OXAPROZIN Pharmacokinetic Parameters

Treatment A = oxaprozin tablets, 600 mg tablet, Dose Administered = 600 mg, fed

Treatment B = Daypro, 600 mg tablet, Dose Administered = 600 mg, fed

Treatment C = oxaprozin tablets, 600 mg tablet, Dose Administered = 600 mg, fasting

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	4527.56	1083.36	4549.79	987.88	4585.32	1197.91	1.00
AUCT	4389.33	996.07	4410.54	915.42	4460.49	1115.72	1.00
CMAX	62.68	7.79	64.50	9.48	61.23	13.71	0.97
KE	0.01	0.00	0.01	0.00	0.01	0.00	1.02
*LAUCI	4407.24	0.24	4449.32	0.22	4430.04	0.28	0.99
*LAUCT	4282.99	0.23	4321.08	0.21	4319.79	0.27	0.99
*LCMAX	62.19	0.13	63.88	0.14	59.58	0.25	0.97
THALF	59.52	14.09	60.18	12.84	58.65	12.90	0.99
TMAX	4.17	1.49	4.61	1.51	4.44	5.08	0.90

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.99	0.99
AUCT	0.98	0.99
CMAX	1.02	1.05
KE	0.99	0.97
*LAUCI	0.99	1.00
*LAUCT	0.99	1.00
*LCMAX	1.04	1.07
THALF	1.01	1.03
TMAX	0.94	1.04

1=Test-NonFast 2=Ref.-NonFast 3=Test-Fast
UNIT: AUC=MCG.HR/ML CMAX=MCG/ML TMAX=HR THALF=HR KE=1/HR
*The values represent the geometric means (antilog of the means of the logs).

Comment on the non-fasting study:
Under non-fasting conditions, the mean plasma oxaprozin acid levels for the test and reference products were comparable to each other as

shown in Table #5 and Figure #2. The ratios of the test mean to the reference mean (RMEAN1/2) for the log-transformed AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25 (Table #5).

Note: The firm conducted the study in two groups of total of 18 subjects. Group-1 included subjects #1, 4, 5, 7-11, and 13-15; and Group-2 included subjects #16-20, 22 and 23.

For statistical analysis, the following are considered:

- The clinical study for the two groups was carried out at the same clinical facility.
- Study subjects in both groups were recruited from the same enrollment pool and have similar demographics.
- All enrolled subjects were randomly assigned to the study treatments.
- Plasma samples from both groups were analyzed as composite study samples by the same analytical facility.

To examine the group effect, the following model used for statistical analysis using the SAS-GLM procedure: subj group per(group) seq trt. No significant group effect was found for the pharmacokinetic parameters LAUCt, LAUCi and LCMAX.
Oxaprozin pharmacokinetic parameters and mean ratios (A/B) re-calculated by the reviewer were in good agreement with the values determined by the sponsor.

Formulation (Not to be released under FOI)
(page #2763, volume C1.7)

Ingredient	**Mg/Tablet (600 mg Strength)**
OXAPROZIN	600
CROSCARMELLOSE SODIUM,	
[redacted] LAURYL SULFATE	
MICROCRYSTALLINE CELLULOSE,	
POVIDONE,	
PURIFIED WATER, USP	
[redacted] OLIDS	
Total theoretical coated weight	let

Formulation Comments: The percentage of the inactive ingredient, [redacted] this formulation is

[redacted]

Dissolution (Not to be released under FOI)

Dissolution Methods / Results

Dissolution Medium: 0.05 M Potassium Phosphate Buffer, pH 7.4+/-0.05 @ 37.0+/-0.5 °C
Volume: 900 mL
Dissolution Apparatus: 2 (paddles)
RPM: 50

Mean Dissolution Data

Test				REFERENCE		
Lot No.: 2C012A				Lot No.: 5K924		
Strength: 600 mg				Strength: 600 mg		
No. of Units: 12				No. of Units: 12		
Time(minutes)	Mean	Range	%CV	Mean	Range	%CV
15	76.5		4.88	65.92		8.37
30	86.75	[illegible]	3.68	76.08		8.78
45	90.08		2.34	82.83		4.48

Dissolution Comments (NOT TO BE RELEASED UNDER FOI)

1. There is no USP dissolution method for oxaprozin tablets. The Division of Bioequivalence has recommended the following method (innovator's method) to other applications (ANDAs #75-842 and #75-850): The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.4, at 37 °C using USP apparatus II (paddle) at 75 rpm.

2. The firm performed dissolution testing for its the test product, oxaprozin tablet in 900 mL of 0.05 M potassium phosphate buffer, pH 7.4, at 37°C using USP apparatus II (paddle) at 50 rpm instead of 1000 mL of 0.05 M phosphate buffer, pH 7.4, at 37 °C using USP apparatus II (paddle) at 75 rpm as recommended by the Division of Bioequivalence. Therefore, dissolution testing performed by the sponsor does not meet Agency specifications.

3. Note: The test and RLD bio-batches #2C012A and #5K924, respectively, are currently expired.

Deficiency:

The firm should conduct the dissolution testing on its test product, oxaprozin tablet in 1000 mL of 0.05 M phosphate buffer, pH 7.4, at 37 °C using USP apparatus II (paddle) at 75 rpm. The dissolution specifications for the test product will be established based on acceptable submitted dissolution data. The dissolution testing should be conducted for both the test and reference products, performed simultaneously. The lot number of the dissolution testing

should be identical to the one used in the in vivo bioeqivalence studies.

Recommendations

1. The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions (studies and), conducted by Mylan Pharmaceuticals on its Oxaprozin Tablet, 600 mg (lot #2C012A), comparing it to the RLD Searle's Daypro® Tablet, 600 mg (lot #5K924), have been found to be incomplete due to the deficiency cited above.

2. The dissolution testing conducted by the firm on its test product Oxaprozin Tablet, 600 mg (lot #2C012A) has been found incomplete due to the deficiency cited above.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT 8/18/00
FT INITIALLED BDAVIT Barbara M Davit 8/18/00

Concur: Dale P. Conner Date: 8/18/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

FIG P-1 . PLASMA OXAPROZIN LEVELS

OXAPROZIN TABLETS, 600 MG, ANDA #75-851
UNDER FASTING CONDITIONS
DOSE=1 X 600 MG

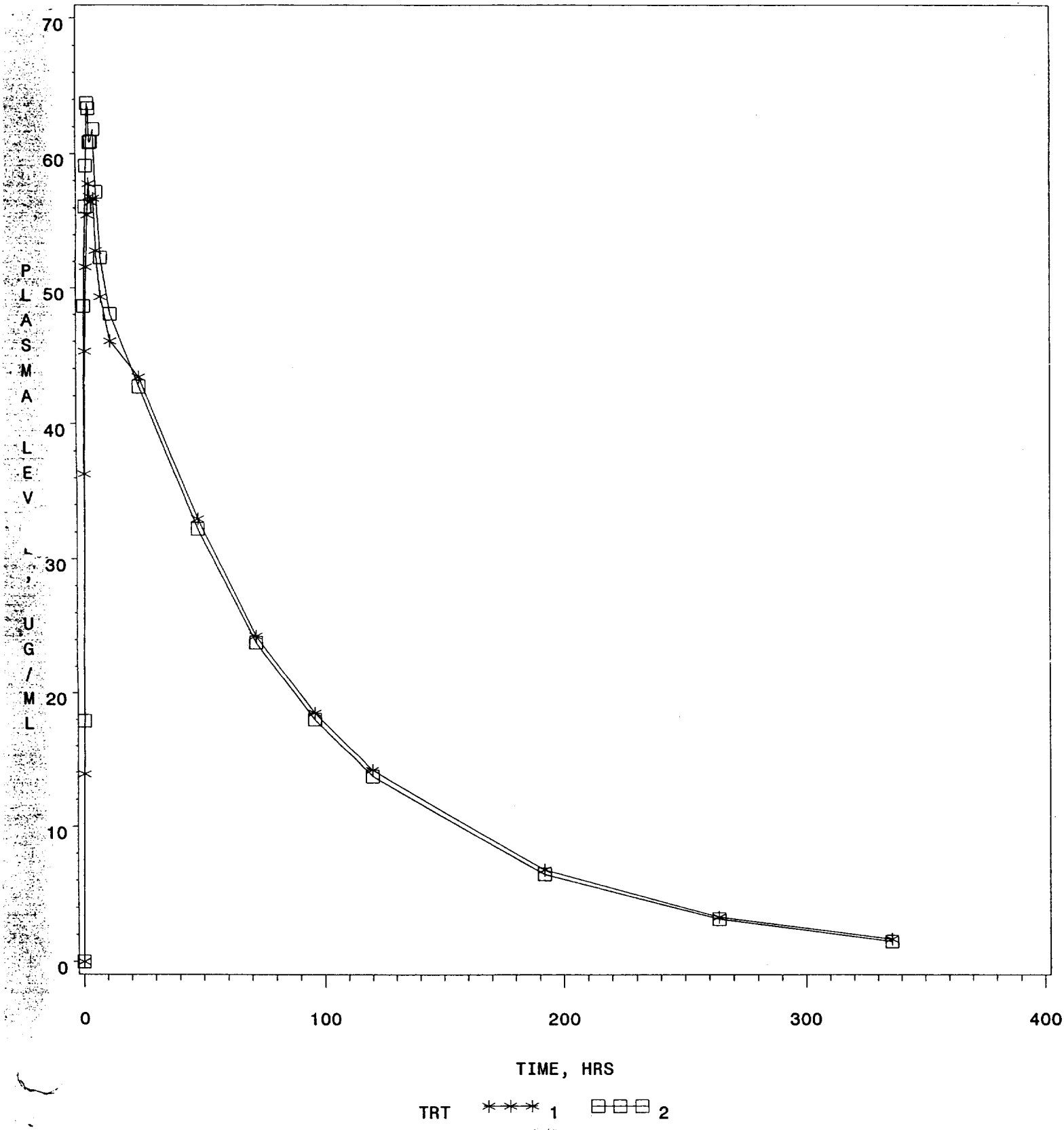
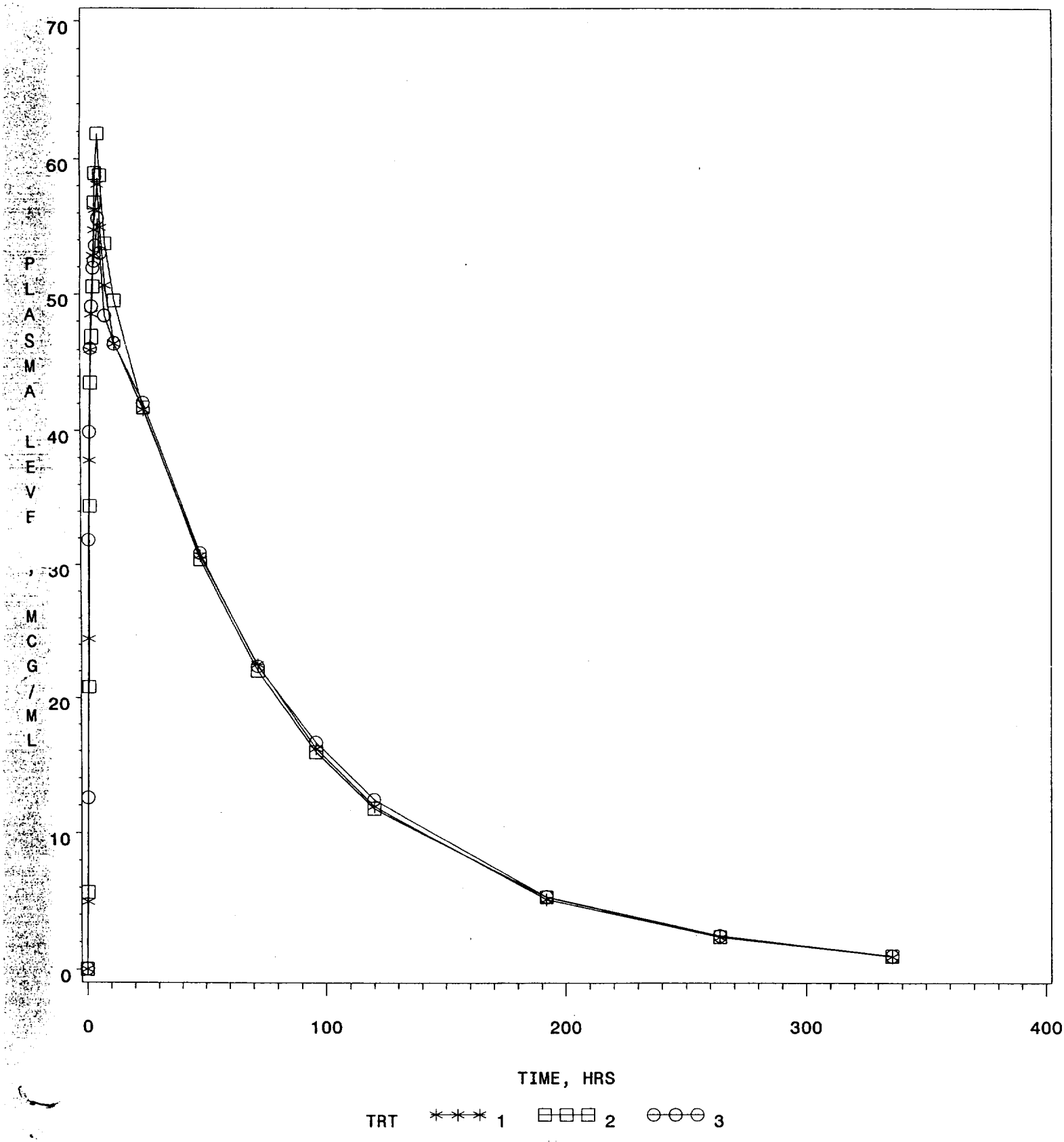


FIG P-2 . PLASMA OXAPROZIN LEVELS

OXAPROZIN TABLET, 600 MG, ANDA #75-851
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 600 MG



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-851

ADMINISTRATIVE DOCUMENTS

OFFICE OF GENERIC DRUGS
ABBREVIATE NEW DRUG APPLICATION

ANDA APPROVAL SUMMARY

ANDA #: 75-851

DRUG PRODUCT: Oxaprozin Tablets

FIRM: Mylan Pharmaceuticals Inc.

DOSAGE: Tablets STRENGTH: 600 mg

cGMP STATEMENT/EIR UPDATE STATUS:
The cGMP Statement located in Volume 1.8 on page 2892 is satisfactory.

The overall recommendation for the Establishment Evaluation Request is Acceptable (November 09, 2000/JDAmbrogio).

BIO STUDY(ies)/BIOEQUIVALENCE STATUS:
The two in-vivo bioequivalence studies, single-dose under fasting and non-fasting conditions, conducted by Mylan Pharmaceuticals on its Oxaprozin Tablets, 600 mg (Lot Nos. 2C012A and R1G2776), comparing it to reference product, Daypro® 600 mg tablets (Lot Nos. 5K924 and 0K793) manufactured by Searle, were found to be acceptable by the Division of Bioequivalence. The studies demonstrated that the Oxaprozin Tablets, 600 mg manufactured by Mylan Pharmaceutical Inc. are bioequivalent to the reference listed drug, Daypro® Tablets, 600 mg. (ZWahba, October 25, 2000)

METHODS VALIDATION (Including dosage form description): The drug substance and the drug product methods have been forwarded to the District Lab for validation.

STABILITY(ARE CONTAINERS USED IN THE STUDY IDENTICAL TO THOSE IN THE CONTAINER CLOSURE SYSTEM):
The containers used in the accelerated and room temperature studies are the same as proposed in the application.

LABELING REVIEW STATUS: Labeling issues have been resolved and all labeling is satisfactory (JBarlow/January 31, 2001).

STERILIZATION VALIDATION (If Applicable): N/A

SIZE OF BIO-BATCH (FIRM'S SOURCE OF NDS O.K.?):

The executed batch size is as follows:

Potency	Batch #	Yield Theoretical	Yield Actual
600 mg	2C012A		

DMF remains adequate.

PROPOSED PRODUCTION BATCH (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):

The proposed batch size is units, which is within the 10X requirement. The manufacturing process for the proposed production batches is comparable.

CHEMIST: David J. Cummings
DATE: July 26, 2001

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-851 SPONSOR : Mylan Pharmaceuticals
DRUG AND DOSAGE FORM : Oxaprozin Tablets STRENGTH(S) : 600 mg
TYPES OF STUDIES : In vivo bioequivalence studies under fasting and non-fasting conditions.
CLINICAL STUDY SITE(S) : Clinical & Pharmacologic Research Inc.
ANALYTICAL SITE(S) : Mylan Pharmaceuticals Inc.

STUDY SUMMARY : The two studies demonstrated that under fasting and non-fasting conditions, Mylan's Oxaprozin Tablets, 600 mg, is bioequivalent to Searle's Daypro® Tablets, 600 mg.

DISSOLUTION : The dissolution data for the test and reference products are acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic New facility ___ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : Z.Z.W. DATE : 10/12/2000

For TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : [signature] DATE : 10/12/2000

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : Barbara M Davit DATE : 10/25/00

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-851

Date of Submission: April 28, 2000

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Oxaprozin Tablet, 600mg

Labeling Deficiencies:

1. **CONTAINER** – Bottles of 100 and 500 tablets
   Satisfactory in **draft** as of the April 28, 2000 submission

2. **INSERT:**
   GENERAL COMMENTS
   a. We encourage you to replace "oxaprozin" with "oxaprozin tablet" throughout the text of the INDICATIONS AND USAGE, CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION sections.

   b. We note that there is a discrepancy between your DESCRIPTION section of the package insert which lists "glyceryl triacetate" as an inactive ingredient and your COMPONENTS AND COMPOSITION STATEMENT which lists "triacetin" as an inactive ingredient. Please revise and/or comment.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-851

CORRESPONDENCE

FA noted, -
To CMC Reviewer
for review.
7/25/01

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 20, 2001

AMENDMENT

FA

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT
(CMC INFORMATION ENCLOSED)

RE: OXAPROZIN TABLETS, 600MG
ANDA 75-851
RESPONSE TO AGENCY CORRESPONDENCE OF JUNE 22, 2001

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the comments pertaining to this application which were provided to Mylan by facsimile in a correspondence dated June 22, 2001 (refer to Attachment K). In response to the comments in the June 22, 2001 correspondence, Mylan wishes to amend its ANDA as follows:

CHEMISTRY DEFICIENCIES

FDA COMMENT 1:

MYLAN RESPONSE:

FDA COMMENT 2:

MYLAN RESPONSE:

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 23 2001

following manner: The (1)were Pract...

...supplier certificate of compliance are provided in Attachment B.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

6/20/01

MYLAN RESPONSE: As requested by the Agency, enclosed in Attachment J is a revised and updated methods validation package (Section XV of the ANDA). This section has been updated to incorporate both the information requested and any changes resulting from the responses submitted in this amendment and our amendment dated January 17, 2001. This information supercedes that submitted in Section XV of the original ANDA.

Also enclosed in separate binders are two additional copies of this updated methods validation package.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures

JUN 22 2001

38. Chemistry comments to be provided to the Applicant.

ANDA: 75-851 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Oxaprozin Tablets, 600 mg

The deficiencies presented below represent **FAX** deficiencies.

Chemistry Deficiencies:

1. Please submit a copy of current drug substance specifications.

2. We acknowledge your response to Comment 3.a. We remind you that you are still responsible for ensuring the identity of the closure material. Please revise the specifications for the caps to include an Identification test. Please note that this may be addressed through your vendor qualification program.

3. Please revise and submit the drug product specifications (release and stability) to identify potential known impurities.

4. Please submit updated long-term stability data.

5. Please submit an update methods validation package (in duplicate) including the following:

   a. a statement of composition of finished dosage forms,
   b. specifications/methods for new drug substances,
   c. specifications/methods for finished dosage form,

d. supporting data/validation reports for the drug substance and drug product, and

e. test results for the new drug substance and dosage form.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

January 17, 2001

NEW CORRESP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT
(CMC INFORMATION INCLUDED)

RE: OXAPROZIN TABLETS, 600MG
ANDA 75-851
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 6, 2000

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the comments pertaining to this application from the Division of Bioequivalence, which were included in the correspondence from the Agency, dated December 6, 2000. In response to the December 6th comments from the Division of Bioequivalence, Mylan wishes to amend this application as follows:

FDA COMMENT 1. The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing will be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.4, at 37°C using USP Apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:
>
> Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

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.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN RESPONSE: The dissolution testing requested by the Division of Bioequivalence will be incorporated into Mylan's stability and quality control programs. Mylan has revised the finished product specifications and dissolution procedure for Oxaprozin Tablets, 600mg to incorporate the requested changes for dissolution. The revised documents are provided in Attachments A and B, respectively.

It is acknowledged and understood that the bioequivalency comments expressed in the correspondence dated December 6, 2000 are preliminary and may be revised after review of the entire application. It is also understood that the 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.

For your reference, a copy of the December 6, 2000 Agency correspondence is provided in Attachment C. Responses to the chemistry comments contained in the December 6th correspondence along with revised labeling, also requested in the Agency's correspondence of December 6, 2000, will be forwarded simultaneously in a separate amendment to this application. The revised finished product specifications, dissolution procedure and post-approval stability protocol will also be included in the CMC amendment.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

ORIG AMENDMENT
N/AC

January 17, 2001

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT
(CMC AND LABELING INFORMATION ENCLOSED)

RE: OXAPROZIN TABLETS, 600MG
ANDA 75-851
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 6, 2000

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Agency's correspondence pertaining to the review of this application dated December 6, 2000 (provided in Attachment T). In response to the Agency's comments of December 6th, Mylan wishes to amend this application as follows.

A. CHEMISTRY DEFICIENCIES

FDA COMMENT 1a:

application.

MYLAN RESPONSE:

Page(s) 15

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

1/17/01

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

B. REGARDING MISCELLANEOUS ISSUES

FDA COMMENT 1: The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current cGMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

MYLAN RESPONSE: Mylan acknowledges that the firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current cGMPs at the time of approval and that an evaluation from the Division of Manufacturing and Product Quality will be requested at the appropriate time.

FDA COMMENT 2: We require a satisfactory methods validation prior to approval of the ANDA. We will schedule the validation with the District Office once the test and specification issues are resolved.

MYLAN RESPONSE: Mylan acknowledges the Agency's comment and also notes that it has not been the Agency's policy to withhold approval of applications pending completion of methods validation. Mylan will provide the information and samples for methods validation upon request. In accordance with the Agency's February 1999 Guidance to Industry, entitled "Organization of an ANDA," Mylan hereby commits to resolve any issues identified in the methods validation process after approval.

FDA COMMENT 3: On page 2909, you make reference to Office of Generic Drugs Policy and Procedure Guide 22-90 – Revised (Dated: 13-SEP-1990). You note that changes will be properly validated and reported to the Agency in the next periodic report. Please note the subject of this document (Subject: Interim Policy on Exceptions to the Batch-Size and Production Condition Requirements for Non-Antibiotic, Solid, Oral-Dosage Form Drug Products Supporting Proposed ANDA's). For purposes of clarity, please note that the 22-90 guide relates to proposed ANDA's. For post-approval changes, it is more appropriate to reference the Guidance for Industry: Changes to an Approved NDA or ANDA.

MYLAN RESPONSE: Mylan acknowledges the reviewer's comment that the Generic Drugs and Procedure Policy Guide 22-90 – Revised (Dated 13-SEP-1990) relates to proposed ANDA's and that for post-approval changes the more appropriate reference is the Guidance for Industry: Changes to an Approved NDA or ANDA.

FDA COMMENT 4: On page 2898, you state "It may be necessary to use additional product identification codes to specifically identify finished dosage units manufactured for a given distributor...." These types of changes should be addressed according to the Guidance for Industry: Changes to an Approved NDA or ANDA. Please acknowledge.

MYLAN RESPONSE: Mylan acknowledges the reviewer's comment that changes to product identification codes to specifically identify finished dosage units manufactured for a given distributor should be addressed according to the current FDA Guidance for Industry: Changes to an Approved NDA or ANDA.

C. REGARDING LABELING DEFICIENCIES

MYLAN RESPONSE: Regarding the labeling deficiencies, Attachment W contains twelve (12) copies of the following final printed bottle labels and outsert for Oxaprozin Tablets, 600mg

BOTTLE LABELS

600mg
Code RM1177A - Bottles of 100 Tablets
Code RM1177B - Bottles of 500 Tablets

OUTSERT
Code OXAP:R1, Revised December 2000

The enclosed labeling incorporates the revisions requested in the Agency's letter of December 6, 2000. A copy of this correspondence is provided in Attachment T for the convenience of the reviewer.

In order to facilitate the review of this labeling, Attachment U contains a side-by-side comparison of the final printed bottle labels to those previously submitted and Attachment V contains a side-by-side comparison of the final printed outsert (OXAP:R1) to the outsert that was previously submitted. It is noted that prior to approval of this application, the Agency may find the color or other factors in the final printed labeling unacceptable and may request further changes to the labeling. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

In the Agency's December 6, 2000 correspondence (included in Attachment T), comments from the Division of Bioequivalence were also provided. These comments listed the dissolution testing requirements for Oxaprozin Tablets, 600mg and acknowledged that these testing requirements will be incorporated into Mylan's stability and quality control programs. A separate amendment, acknowledging the comments from the Division of Bioequivalence will be forwarded simultaneously with this CMC amendment.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures

G:\PROJECT\ANDA\OXAPROZIN\MAJOR-AGENCY-LETTER-DATED-120600.doc

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-851
APPLICANT: Mylan Pharmaceuticals
DRUG PRODUCT: Oxaprozin Tablets, 600 mg

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

We acknowledge that the following dissolution testing will be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.4, at 37 °C using USP apparatus II (Paddle) at 75 rpm. The test product should meet the following specifications:
>
> Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

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,

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

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

OCT 6 2000

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
(BIOEQUIVALENCE DATA ENCLOSED)

NEW CORRESP

RE: OXAPROZIN TABLETS, 600MG
ANDA 75-851
(RESPONSE TO AGENCY TELEPHONE REQUEST OF OCTOBER 3, 2000)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to an October 3, 2000 telephone call from the Division of Bioequivalence requesting clarification on Mylan's September 5, 2000 Bioequivalence Amendment. In response to the Agency's September 5th telephone request, Mylan wishes to amend the application as follows:

FDA COMMENT 1: Provide the manufacturing date for the current test product, Mylan Oxaprozin Tablets, 600mg, Lot R1G2776.

MYLAN RESPONSE: The manufacturing date for Mylan's current batch of Oxaprozin Tablets, 600mg, Lot R1G2776 is April 25, 2000.

FDA COMMENT 2: Clarify the lot number for the current reference drug, Daypro® Tablets: Page 11 of the Amendment refers to Lot 0K793, page 12 of the Amendment refers to Lot OK793.

MYLAN RESPONSE: The correct lot number for the current reference product, Daypro® Tablets is 0K793 as reflected on page 11 of the September 9th Amendment. The dissolution profile for this product has been revised to reflect the correct lot number and is provided in Attachment A.

FDA COMMENT 3: Confirm that the expiration date of the current reference product is February 2003.

MYLAN RESPONSE: The expiration date for the current reference product, Daypro® Tablets, Lot 0K793 is February 2003. A copy of the Daypro® bottle label that displays the expiration date is provided in Attachment B.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures

cc: Mr. Steve Mazzella (via facsimile)

DEC -6 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-851 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Oxaprozin Tablets, 600 mg

The deficiencies presented below represent **MAJOR** deficiencies.

A. Chemistry Deficiencies:

1. The following comments pertain to your raw material controls:

a.

b.

c.

d.

e.

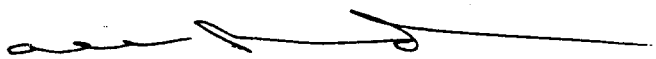
f.

Page(s) 4

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

4. On page 2898, you state "It may be necessary to use additional product identification codes to specifically identify finished dosage units manufactured for a given distributor…." These types of changes should be addressed according to the Guidance for Industry: Changes to an Approved NDA or ANDA. Please acknowledge.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-851
APPLICANT: Mylan Pharmaceuticals
DRUG PRODUCT: Oxaprozin Tablets, 600 mg

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

We acknowledge that the following dissolution testing will be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.4, at 37 °C using USP apparatus II (Paddle) at 75 rpm. The test product should meet the following specifications:
>
> Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

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,

Barbara M Davis

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

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

APR 28 2000

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXAPROZIN TABLETS, 600MG

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Oxaprozin Tablets
This application consists of a total of 21 volumes.
Archival Copy - 9 volumes.
Review Copy - 10 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 7 volumes.
Analytical Methods - 2 extra copies; 1 volume each.
NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies conducted in support of this application. In addition, the diskettes providing the Bioequivalence Electronic Submission ESD (BA/BE) EVA will be forwarded to the Agency within the 30 day grace period.

This application provides for the manufacture of Oxaprozin Tablets, 600mg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

G:\PROJECT\ANDA\OXAPROZIN\SECTIONS-01THRU07.doc

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Marilyn A. Fiedler for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

ANDA 75-851

Mylan Pharmaceutical Inc.
Attention: Frank Sisto
781 Chestnut Ridge Road
P.O. BOX 4310
Morgantown, WV 26504-4310

MAY 22 2000

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.

NAME OF DRUG: Oxaprozin Tablets, 600 mg

DATE OF APPLICATION: April 28, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 1, 2000

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:

Bonnie McNeal
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG 29 2000

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-851
APPLICANT: Mylan Pharmaceuticals
DRUG PRODUCT: Oxaprozin Tablets, 600 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified.

You are advised to re-submit dissolution data applying the following conditions: Conduct the dissolution testing on your test product, Oxaprozin Tablets in 1000 mL of 0.05 M phosphate buffer, pH 7.4, at 37 °C using USP apparatus II (paddle) at 75 rpm. The dissolution specifications for your test product will be established based on acceptable submitted dissolution data. The dissolution testing should be conducted for both the test and reference products, performed simultaneously. We acknowledge that the bio-batches of the test and reference products have expired. Please submit dissolution testing data using both the bio-batches and current batches of test and reference products.

Sincerely yours,

Dale P. Conner

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-851
APPLICANT: Mylan Pharmaceuticals
DRUG PRODUCT: Oxaprozin Tablets, 600 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified.

You are advised to re-submit dissolution data applying the following conditions: Conduct the dissolution testing on your test product, Oxaprozin Tablets in 1000 mL of 0.05 M phosphate buffer, pH 7.4, at 37 °C using USP apparatus II (paddle) at 75 rpm. The dissolution specifications for your test product will be established based on acceptable submitted dissolution data. The dissolution testing should be conducted for both the test and reference products, performed simultaneously. We acknowledge that the bio-batches of the test and reference products have expired. Please submit dissolution testing data using both the bio-batches and current batches of test and reference products.

Sincerely yours,

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