CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 75078

Trade Name Etodolac Capsules 200mg and 300mg

Generic Name Etodolac Capsules 200mg and 300mg

Sponsor Taro Pharmaceuticals, U.S.A. Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 75078

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x **CENTER FOR DRUG EVALUATION AND RESEARCH**

Application Number 75078

APPROVAL LETTER

ANDA 75-078

APR 30 1998

Taro Pharmaceuticals, U.S.A., Inc.
Attention: Lorraine W. Sachs
U.S. Agent for: Taro Pharmaceutical Industries, Ltd.
Five Skyline Drive
Hawthorne, New York 10532

Dear Madam:

This is in reference to your abbreviated new drug application dated February 14, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etodolac Capsules 200 mg and 300 mg.

Reference is also made to your amendments dated February 19, March 27, April 1, April 10, June 9, June 17, and September 8, 1997; and February 6, March 24 and April 9, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Etodolac Capsules 200 mg and 300 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lodine® Capsules 200 mg and 300 mg, respectively, of Wyeth-Ayerst Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

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

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

Sincerely yours,

Douglas L. Sporn 4/30/98
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75078

FINAL PRINTED LABELING

TARO

APPROVED

APR 30 1998

Etodolac

Capsules

300 mg

Caution:
Federal law prohibits dispensing without prescription.

100 Capsules

Sealed for your protection

NDC 51672-4017-1

Dispense in a well-closed container as defined in the USP.
Store at controlled room temperature, 15°-30°C (59°-86°F), protected from moisture.

Usual Dosage:
See accompanying package insert.

Each capsule contains: Etodolac 300 mg

Manufactured by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Distributed by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

3 0 1998

APPROVED

Etodolac

Capsules

200 mg

Caution:
Federal law prohibits dispensing without prescription.

100 Capsules

Sealed for your protection

NDC 51672-4016-1

Dispense in a well-closed container as defined in the USP.
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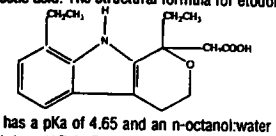
Hawthorne, NY 10532

Etodolac Capsules

Description

Etodolac Capsules are a pyranocarboxylic acid chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The structural formula for etodolac is shown below:



Molecular Weight: 287.37

Molecular Formula: $C_{17}H_{21}NO_3$

It has a pKa of 4.65 and an n-octanol:water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

Each Capsule, for oral administration, contains 200 or 300 mg of Etodolac. In addition, each capsule contains the following inactive ingredients: Ammonium Hydroxide USP, Black Iron Oxide USP, Colloidal Silicone Dioxide NF, Erythrosine (200 mg only), Ethyl Alcohol USP, Gelatin, Isopropyl Alcohol USP, Lactose Monohydrate NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, N-Butyl Alcohol USP, Povidone USP, Propylene Glycol USP, Purified Water USP, Shellac, Titanium Dioxide.

Clinical Pharmacology

PHARMACOLOGY

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac, like that of other NSAIDs, is not known but is believed to be associated with the inhibition of prostaglandin biosynthesis.

Etodolac is a racemic mixture of [-]R- and [+]S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the [+]S-form is biologically active. Both enantiomers are stable and there is no [-]R to [+]S conversion *in vivo*.

PHARMACODYNAMICS

Analgesia was demonstrable 1/2 hour following single doses of 200 to 400 mg etodolac, with the peak effect occurring in 1 to 2 hours. The analgesic effect generally lasted for 4 to 6 hours (see **Clinical Pharmacology,** Clinical Trials).

PHARMACOKINETICS

The pharmacokinetics of etodolac have been evaluated in 267 normal subjects, 44 elderly patients (>65 years old), 19 patients with renal failure (creatinine clearance 37 to 88 mL/min), 9 patients on hemodialysis, and 10 patients with compensated hepatic cirrhosis. Etodolac, when administered orally, exhibits kinetics that are well described by a two-compartment model with first-order absorption. Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin, glyburide, furosemide or hydrochlorothiazide.

Absorption

Etodolac is well absorbed and had a relative bioavailability of 100% when 200 mg capsules were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from either the tablet or capsule formulation, is at least 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. Mean (± 1 SD) peak plasma concentrations range from approximately 14 ± 4 to 37 ± 9 mcg/mL after 200 to 600 mg single doses and are reached in 80 ± 30 minutes (see Table 1 for summary of pharmacokinetic parameters). The dose-proportionality based on AUC (the area under the plasma concentration-time curve) is linear following doses up to 600 mg every 12 hours. Peak concentrations are dose proportional for both total and free etodolac following doses up to 400 mg every 12 hours, but following a 600 mg dose, the peak is about 20% higher than predicted on the basis of lower doses.

Table 1. Etodolac Steady-State Pharmacokinetic Parameters (N=267)

Kinetic Parameters	Mean ± SD
Extent of oral absorption (bioavailability)	[F] ≥ 80%
Oral-dose clearance [CL/F]	47 ± 16 mL/h/kg
Steady-state volume [V_{ss}/F]	362 ± 129 mL/kg
Distribution half-life [$t_{1/2}$, α]	0.71 ± 0.50 h
Terminal half-life [$t_{1/2}$, β]	7.3 ± 4.0 h

Antacid Effects

The extent of absorption of etodolac is not affected when etodolac is administered with an antacid. Coadminsitration with an antacid decreases the peak concentration reached by about 15 to 20%, with no measurable effect on time-to-peak.

Food Effects

The extent of absorption of etodolac is not affected when etodolac is administered after a meal. Food intake, however, reduces the peak concentration reached by approximately one half and increases the time-to-peak concentration by 1.4 to 3.8 hours.

Distribution

Etodolac has an apparent steady-state volume of distribution about 0.362 L/kg. Within the therapeutic dose range, etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied.

Metabolism

Etodolac is extensively metabolized in the liver, with renal elimination of etodolac and its metabolites being the primary route of excretion. The intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

Protein Binding

Data from *in vitro* studies, using peak serum concentrations at reported therapeutic doses in humans, show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.

Elimination

The mean plasma clearance of etodolac, following oral dosing is 47 (± 16) mL/h/kg, and terminal disposition half-life is 7.3 (± 4.0) hours. Approximately 72% of the administered dose is recovered in the urine as the following, indicated as % of the administered dose:

-etodolac, unchanged	1%
-etodolac glucuronide	13%
-hydroxylated metabolites (6-, 7-, and 8-OH)	5%
-hydroxylated metabolite glucuronides	20%
-unidentified metabolites	33%

Fecal excretion accounted for 16% of the dose.

SPECIAL POPULATIONS

Elderly Patients

In clinical studies, etodolac clearance was reduced by about 15% in older patients (>65 years of age). In these studies, age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, on the basis of body size (see **Precautions** - GERIATRIC POPULATION), as they may be more sensitive to antiprostaglandin effects than younger patients (see **Precautions** - GERIATRIC POPULATION).

Renal Impairment

Studies in patients with mild-to-moderate renal impairment (creatinine clearance 37 to 88 mL/min) showed no significant differences in the disposition of total and free etodolac. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac, due to a 50% greater unbound fraction. Free etodolac clearance was not altered, indicating the importance of protein binding in etodolac's disposition. Nevertheless, etodolac is not dialyzable.

Hepatic Impairment

In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Although no dosage adjustment is generally required in this patient population, etodolac clearance is dependent on hepatic function and could be reduced in patients with severe hepatic failure.

CLINICAL TRIALS

Analgesia

Controlled clinical trials in analgesia were single-dose, randomized, double-blind, parallel studies in three pain models, including dental extractions. The analgesic effective dose for etodolac established in these acute pain models was 200 to 400 mg. The onset of analgesia occurred approximately 30 minutes after oral administration. Etodolac 200 mg provided efficacy comparable to that obtained with aspirin (650 mg). Etodolac 400 mg provided efficacy comparable to that obtained with acetaminophen with codeine (600 mg + 60 mg). The peak analgesic effect was between 1 to 2 hours. Duration of relief averaged 4 to 5 hours for 200 mg of etodolac and 5 to 6 hours for 400 mg of etodolac as measured by when approximately half of the patients required remedication.

Osteoarthritis

The use of etodolac in managing the signs and symptoms of osteoarthritis of the hip or knee was assessed in double-blind, randomized, controlled clinical trials in 341 patients. In patients with osteoarthritis of the knee, etodolac, in doses of 600 to 1000 mg/day, was better than placebo in two studies. The clinical trials in osteoarthritis used b.i.d. dosage regimens.

Indications and Usage

Etodolac is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis. Etodolac is also indicated for the management of pain.

Contraindications

Etodolac is contraindicated in patients with known hypersensitivity to etodolac. Etodolac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to etodolac have been reported in such patients (see **Warnings** - ANAPHYLACTOID REACTIONS).

Warnings

RISK OF GASTROINTESTINAL (GI) ULCERATION, BLEEDING, AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) THERAPY

Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of such agents for several months' to 2 years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appears 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.

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

ANAPHYLACTOID REACTIONS

Anaphylactoid reactions may occur in patients without prior exposure to etodolac. Etodolac should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other nonsteroidal anti-inflammatory drugs. Fatal reactions have been reported in such patients (see **Contraindications** and **Precautions** - Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

ADVANCED RENAL DISEASE

In cases with advanced kidney disease, as with other NSAIDs, treatment with etodolac should only be initiated with close monitoring of the patient's kidney function (see **Precautions** - Renal Effects).

PREGNANCY

In late pregnancy, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus (see **Precautions** - Teratogenic Effects - Pregnancy Category C).

Precautions

GENERAL PRECAUTIONS

Renal Effects

As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study. A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction; those taking diuretics; and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state. Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in **Adverse Reactions**) may be attributable to these metabolites should be considered.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including etodolac. These abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Meaningful elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with etodolac. 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 a more severe hepatic reaction while on therapy with etodolac. Rare cases of liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), etodolac should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs including etodolac. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including etodolac, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs, including etodolac. Therefore, etodolac should be used with caution in patients with fluid retention, hypertension, or heart failure.

Pre-existing Asthma

About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between

aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, etodolac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

INFORMATION FOR PATIENTS

Etodolac, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

Physicians may wish to discuss with their patients the potential risks (see **Warnings, Precautions, Adverse Reactions**) and likely benefits of nonsteroidal anti-inflammatory drug treatment.

Patients on etodolac should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Because serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this follow-up (see **Warnings** - RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY THERAPY).

Patients should also be instructed to seek medical emergency help in case of an occurrence of anaphylactoid reactions (see **Warnings**).

LABORATORY TESTS

Patients on long-term treatment with etodolac, as with other NSAIDs, should have their hemoglobin or hematocrit checked periodically for signs or symptoms of anemia. Appropriate measures should be taken in case such signs of anemia occur.

If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g., eosinophilia, rash, etc.) and if abnormal liver tests are detected, persist or worsen, etodolac should be discontinued.

DRUG INTERACTIONS

Antacids

The concomitant administration of antacids has no apparent effect on the extent of absorption of etodolac. However, antacids can decrease the peak concentration reached by 15% to 20% but have no detectable effect on the time-to-peak.

Aspirin

When etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free etodolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.

Warfarin

Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and etodolac results in reduced protein binding of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and etodolac should not require dosage adjustment of either drug. However, there have been a few spontaneous reports of prolonged prothrombin times in etodolac-treated patients receiving concomitant warfarin therapy. Caution should be exercised because interactions have been seen with other NSAIDs.

Cyclosporine, Digoxin, Lithium, Methotrexate

Etodolac, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels of digoxin, lithium, and methotrexate and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs.

Phenylbutazone

Phenylbutazone causes increase (by about 80%) in the free fraction of etodolac. Although *in vivo* studies have not been done to see if etodolac clearance is changed by coadministration of phenylbutazone, it is not recommended that they be coadministered.

DRUG/LABORATORY TEST INTERACTIONS

The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose relationship has been observed.

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dL were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m², respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3.0 to 5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 mcg/mL) compared to negative controls (2.0%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m²). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

PREGNANCY

Teratogenic Effects - Pregnancy Category C

In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2 to 14 mg/kg/day) close to human clinical doses. However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose-response relationship.

There are no adequate or well-controlled studies in pregnant women. Etodolac should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arteriosus, use during late pregnancy should be avoided.

LABOR AND DELIVERY

In rat studies with etodolac, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of etodolac on labor and delivery in pregnant women are unknown.

NURSING MOTHERS

It is not known whether etodolac is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etodolac, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC POPULATION

As with any NSAID, however, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose because the elderly seem to tolerate NSAID side effects less well than younger patients. In patients 65 years and older, no substantial differences in the side effect profile of etodolac were seen compared with the general population (see **Clinical Pharmacology** - PHARMACOKINETICS).

Adverse Reactions

Adverse-reaction information for etodolac was derived from 2,629 arthritic patients treated with etodolac in double-blind and open-label clinical trials of 4 to 320 weeks in duration and worldwide postmarketing surveillance studies. In clinical trials, most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials, because of adverse events, was up to 10% for patients treated with etodolac.

New patient complaints (with an incidence greater than or equal to 1%) are listed below by body system. The incidences were determined from clinical trials involving 465 patients with osteoarthritis treated with 300 to 500 mg of etodolac b.i.d. (i.e., 600 to 1000 mg/day).

INCIDENCE GREATER THAN OR EQUAL TO 1% - PROBABLY CAUSALLY RELATED

Body as a whole - Chills and fever.

Digestive system - Dyspepsia (10%), abdominal pain*, diarrhea*, flatulence*, nausea*, constipation, gastritis, melena, vomiting.

Nervous system - Asthenia/malaise*, dizziness*, depression, nervousness.

Skin and appendages - Pruritus, rash.

Special senses - Blurred vision, tinnitus.

Urogenital system - Dysuria, urinary frequency.

* Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac.

Drug-related patient complaints occurring in fewer than 3%, but more than 1%, are unmarked.

INCIDENCE LESS THAN 1% - PROBABLY CAUSALLY RELATED

(Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized.)

Body as a whole - *Allergic reaction, anaphylactoid reaction.*

Cardiovascular system - Hypertension, congestive heart failure, flushing, palpitations, syncope, *vasculitis (including necrotizing and allergic).*

Digestive system - Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, *cholestatic hepatitis,* hepatitis, *cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis,* peptic ulcer with or without bleeding and/or perforation, *intestinal ulceration, pancreatitis.*

Hemic and lymphatic system - Ecchymosis, anemia, thrombocytopenia, bleeding time increased, *agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.*

Metabolic and nutritional - Edema, serum creatinine increase, *hyperglycemia in previously controlled diabetic patients.*

Nervous system - Insomnia, somnolence.

Respiratory system - Asthma.

Skin and appendages - Angioedema, sweating, urticaria, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome,* hyperpigmentation, *erythema multiforme.*

Special senses - Photophobia, transient visual disturbances.

Urogenital system - *Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.*

INCIDENCE LESS THAN 1% - CAUSAL RELATIONSHIP UNKNOWN

(Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians.)

Body as a whole - Infection, headache.

Cardiovascular system - Arrhythmias, myocardial infarction, cerebrovascular accident.

Digestive system - Esophagitis with or without stricture or cardiospasm, colitis.

Metabolic and nutritional - Change in weight.

Nervous system - Paresthesia, confusion.

Respiratory system - Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis.

Skin and appendages - Alopecia, maculopapular rash, photosensitivity, skin peeling.

Special senses - Conjunctivitis, deafness, taste perversion.

Urogenital system - Cystitis, hematuria, leukorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities.

Overdosage

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur and coma has occurred following massive ibuprofen or mefenamic-acid overdose. Hypertension, acute renal failure, and respiratory depression may occur but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following overdose.

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, alkalinization of the urine, hemodialysis, or hemoperfusion would probably not be useful due to etodolac's high protein binding.

Dosage and Administration

As with other NSAIDs, the lowest dose and longest dosing interval should be sought for each patient. Therefore, after observing the response to initial therapy with etodolac, the dose and frequency should be adjusted to suit an individual patient's needs.

Dosage adjustment of etodolac is generally not required in patients with mild to moderate renal impairment. Etodolac should be used with caution in such patients, because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function (see **Precautions** - GENERAL PRECAUTIONS, Renal Effects).

ANALGESIA

The recommended total daily dose of etodolac for acute pain is up to 1000 mg, given as 200-400 mg every 6 to 8 hours. In some patients, if the potential benefits outweigh the risks; the dose may be increased to 1200 mg/day in order to achieve a therapeutic benefit that might not have been achieved with 1000 mg/day. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled trials.

OSTEOARTHRITIS

The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis is: 300 mg b.i.d., t.i.d., or 400 mg b.i.d., or 500 mg b.i.d. During long-term administration, the dose of etodolac may be adjusted up or down depending on the clinical response of the patient. A lower dose of 600 mg/day may suffice for long-term administration. In patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. When treating patients with higher doses, the physician should observe sufficient increased clinical benefit to justify the higher dose. Physicians should be aware that doses above 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

In chronic conditions, a therapeutic response to therapy with etodolac is sometimes seen within one week of therapy, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

How Supplied

Etodolac Capsules are available as:

200 mg capsules (dark pink, black body and cap imprinted with "ETO 200")

- in bottles of 100, NDC 51672-4016-1

300 mg capsules (pink, black body and cap imprinted with "ETO 300")

- in bottles of 100, NDC 51672-4017-1

Store at controlled room temperature 15°-30°C (59°-86°F), protected from moisture.

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

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by: **Taro Pharmaceutical Industries Ltd.**
Haifa Bay, Israel 26110
Issued: July 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75078

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA# 75-078

3. NAME AND ADDRESS OF APPLICANT
Taro Pharmaceuticals U.S.A., Inc.
Attention: Lorraine W. Sachs, RAC
Five Skyline Drive
Hawthorne, NY 10532

4. LEGAL BASIS FOR SUBMISSION
Based on Wyeth-Ayerst Laboratories' Lodine ® Capsules 200 and 300 mg. Patent expired on 2/28/97.

5. SUPPLEMENT(s) N/A 6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Etodolac Capsules

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

9. AMENDMENTS AND OTHER DATES:

2/14/97	Orig. application submitted.
2/19/97	New corr.(Bio)
3/27/97	Tel. amendment
4/1/97	New corr.
4/10/97	Corr.(Bio)
6/9/97	New corr.(Bio)
6/17/97	New corr.(Bio)
9/8/97	Amendment (This review)
2/6/98	Tel.amendment
3/24/98	Amendment (Labeling)
4/9/98	Tel.amendment (This review)

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC
Anti-inflammatory Rx

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER: DATE COMPLETED:
J.Fan 3/4/98
4/16/98 (Revised)

cc: ANDA 75-078
ANDA DUP
DIV FILE
Field Copy
Reading file

Endorsements:
HFD-623/J.Fan/ 4/16/98
HFD-623/V.Sayeed, Ph.D./
x:\new\firmsnz\taro\ltrs&rev\75078n2.d
F/t by: bc/4-16-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75078

BIOEQUIVALENCE REVIEW(S)

ANDA 75-078

SEP 29 1997

Taro Pharmaceuticals USA, Inc.
Attention: Timothy A. Anderson
U.S. Agent for: Taro Pharmaceuticals Inc.
5 Skyline Drive
Hawthorne, NY 10532

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Etodolac Capsules 200 and 300 mg.

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

2. The following dissolution testing will need to be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 1000 mL of 0.1 M phosphate buffer, pH 7.5, at 37°C using USP 23 Apparatus 1 (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than [redacted]) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 14 1997

Etodolac Capsules	Taro
200 mg and 300 mg Capsules	Hawthorne, NY
ANDA #75-078	Submission Date:
Reviewer: Moo Park	2/14/1997; 6/17/97
Filename: 75078sdw.297	

Review of Two *In Vivo* Bioequivalence Studies, Dissolution Data and Waiver Request

I. Objective

Review of Taro's ANDA #75-078. The submission contains the following:

1. Randomized, single-dose, 2-way crossover *in vivo* bioequivalence study comparing Taro's Etodolac Capsules, 300 mg strength, to Wyeth-Ayerst's Lodine^{R}, 300 mg strength, in healthy adult males under fasting conditions.

2. Randomized, single-dose, 3-way crossover *in vivo* bioequivalence study comparing Taro's Etodolac Capsules, 300 mg strength, to Wyeth-Ayerst's LodineR, 300 mg strength, in healthy adult males under nonfasting/fasting conditions.

3. Dissolution testing data for the 200 mg and 300 mg capsules.

4. Waiver request for the 200 mg capsules.

II. Background

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) used for the treatment of osteoarthritis and for the management of pain. Etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration. The systemic availability of etodolac is at least 80% and the drug does not undergo significant first-pass metabolism. Etodolac is well absorbed after an oral dose with peak plasma levels obtained at about 80 minutes after dosing to fasted subjects. The terminal half-life is about 7 hours. Intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

The extent of absorption of etodolac is not affected when etodolac is administered after a meal or with an antacid. Food intake, however, reduces the peak concentration by approximately one half and increases the time to peak concentration by 1.4 to 3.8 hours.

The recommended dose of etodolac for acute pain is 200 to 400 mg every 6 to 8 hours, as needed, not to exceed a total daily dose of 1200 mg. Lodine[R] (Wyeth-Ayerst) is the innovator product and marketed strengths include 200 and 300 mg capsules, and 400 and 500 mg tablets.

III. Study Details

A. Study under Fasting Conditions

Protocol No.

Applicant Taro

Study sites

Investigators

Study dates 8/1/96-8/9/96

Study design Open-label, randomized, two period, two treatment, crossover study.

Subjects 26 subjects were enrolled in the study. Subject No. 25 withdrew from the study 2.4 hours after Period 1 dosing due to difficulty with the subject's vein. Thus a total of 25 subjects completed the crossover.

Drug products
1. Test product: Taro's Etodolac Capsules, 300 mg strength, Lot #960645.
2. Reference product: Wyeth-Ayerst's Lodine[R], 300 mg strength, Lot #3950568; Expiration 3/98

Dosing	Single oral dose of 300 mg capsules with 240 mL of water.
Food and fluid	Prior to each period there was an overnight fast of at least 10 hours. Water (240 mL at room temperature) was consumed at the time of dosing and water was restricted 1 hour before and 1 hour after the dose, but after which there was no restriction. Four (4) and 9 hours after dosing standardized meals were served.
Housing	Subjects were admitted to the research center the evening prior to dosing and were discharged after the 30-hour after dosing blood sample was obtained.
Washout	One week.
Blood samples	During each period, plasma samples were obtained from blood drawn into EDTA tubes at 0 (pre-dose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, and 30 hours after administration of the dose. The blood samples were centrifuged under refrigeration. Plasma collected was stored at -12°C or lower until assayed.
IRB	
Informed consent	The form was signed by each subject prior to enrollment.
Assay method for blood samples	
Analytes	Etodolac in plasma
PK analysis	AUCT, AUCI, CMAX, TMAX, KE, and THALF were calculated.
Statistical analysis	90% confidence intervals for log-transformed and untransformed AUCT, AUCI, and CMAX were calculated.

B. Study under Nonfasting Conditions

Protocol No.	
Applicant	Taro
Study sites	
Investigators	
Study dates	8/28/96-9/12/96
Study design	Open-label, randomized, three period, three treatment, crossover study.
Subjects	18 subjects were enrolled in the study and completed the three period study.
Drug products	1. Test product under fasting: Taro's Etodolac Capsules, 300 mg strength, Lot #960645. 2. Test product under nonfasting: Taro's Etodolac Capsules, 300 mg strength, Lot #960645. 3. Reference product under nonfasting: Wyeth-Ayerst's Lodine^{R}, 300 mg strength, Lot #3950568; Expiration 3/98
Dosing	Single oral dose of 300 mg capsules with 240 mL of water.
Food and fluid	Prior to each period there was an overnight fast of at least 10 hours. Subjects on Regimen 1 fasted until 4 hours post dosing. Subjects on Regimens 2 and 3 fasted until 30 minutes prior to their scheduled dosing times, when they were given a standard breakfast. Four (4) hours after dosing a standardized meal was served. Meals plans were identical for all periods.
Housing	Subjects were admitted to the research center the evening prior to dosing and were discharged after the 30-hour blood sample was obtained.
Washout	One week.

Blood samples	During each period, plasma samples were obtained from blood drawn into EDTA tubes at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, and 30 hours after administration of the dose. The blood samples were centrifuged under refrigeration. Plasma collected was stored at -12°C or lower until assayed.
IRB	
Informed consent	The form was signed by each subject prior to enrollment.
Assay method for blood samples	
Analytes	Etodolac in plasma
PK analysis	AUCT, AUCI, CMAX, TMAX, KE, and THALF were calculated.
Statistical analysis	Test/Reference ratios under nonfasting conditions for log-transformed and untransformed AUCT, AUCI, and CMAX were calculated.

IV. Bioanalytical Method Validation

A. Pre-study Validation

V. Pharmacokinetic and Statistical Evaluation of Study Data

A. Study under Fasting Conditions

Subjects: 26 subjects were enrolled in the study. Subject No. 25 withdrew from the study 2.4 hours after Period 1 dosing due to difficulty with the subject's vein. Thus a total of 25 subjects completed the crossover. Data from 24 subjects (Subjects #1-24) were used in the pharmacokinetic/statistical evaluation per protocol.

Medical events: A total of 5 medical events (2 for test product and 3 for reference product.) were reported. No serious medical events were reported during the study.

Evaluation of study data: Reviewer recalculated all the pharmacokinetic parameters and statistics and the results of the recalculation are in agreement with the sponsor's submission.

1. Mean plasma etodolac levels

Mean plasma etodolac levels for the test and reference products under fasting conditions were comparable to each other as shown in Table V-A-1 and Fig. P-1. Peak mean plasma levels for the test and reference products were 16.9 mcg/mL at 1.67 hours and 18.2 mcg/mL at 1 hour, respectively.

TABLE V-A-1. MEAN PLASMA Etodolac LEVELS FOR TEST AND REFERENCE PRODUCTS UNDER FASTING CONDITIONS
UNIT: PLASMA LEVEL=MCG/ML TIME=HRS
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO
SD=STANDARD DEVIATION
Test Lot #960645; Ref Lot #3950568

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	1.28	1.99	2.68	3.31	0.48
0.67	10.53	7.51	14.92	9.68	0.71
1	14.71	8.00	18.20	8.77	0.81
1.33	16.18	7.78	17.42	7.41	0.93
1.67	16.89	6.63	15.74	5.45	1.07
2	15.43	6.24	14.68	4.70	1.05
2.5	13.18	4.84	13.79	4.91	0.96
3	12.86	3.97	12.25	3.90	1.05
4	11.04	4.28	9.27	2.37	1.19
6	5.29	1.75	5.26	2.23	1.01
8	4.28	1.57	4.27	1.71	1.00
12	3.15	1.29	3.14	1.34	1.00
16	2.00	1.02	2.21	1.09	0.91
24	0.94	0.67	0.96	0.82	0.98
30	0.34	0.54	0.38	0.61	0.90

2. PK parameters and 90% confidence intervals

The arithmetic and geometric means for the PK parameters are shown in Table V-A-2. PK parameters, AUCT, AUCI, CMAX, LAUCT, LAUCI, and LCMAX for the test and reference products are comparable to each other. Their Test/Reference ratios range 0.98-1.0.

Table V-A-3 shows the LSMEANS for the test and reference products and the 90% confidence intervals for AUCT, AUCI and CMAX. The LSMEANS are comparable for the test and reference products and the 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within the acceptable range of 80-125%.

Sequence effect was observed for LAUCT.

TABLE V-A-2. ARITHMETIC/GEOMETRIC MEANS AND RATIOS
UNDER FASTING CONDITIONS
UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO
SD=STANDARD DEVIATION

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	122.95	35.81	125.91	35.88	0.98
AUCT	112.80	32.60	113.93	31.15	0.99
CMAX	22.88	4.88	23.38	6.20	0.98
KE	0.10	0.02	0.10	0.03	0.98
LAUCI	118.23	0.28	121.14	0.28	0.98
LAUCT	108.45	0.29	109.95	0.27	0.99
LCMAX	22.37	0.22	22.47	0.30	1.00
THALF	7.36	1.27	7.51	1.79	0.98
TMAX	1.81	1.06	1.68	1.19	1.08

TABLE V-A-3. LSMEANS AND 90% CONFIDENCE INTERVALS
UNDER FASTING CONDITIONS
UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
LSM1=TEST; LSM2=REFERENCE; RLSM12=LSM1/LSM2 RATIO
LOWCI12=LOWER 90% CI; UPPCI12=UPPER 90% CI

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	122.95	125.10	0.98	94.11	102.44
AUCT	112.80	113.93	0.99	94.86	103.17
CMAX	22.88	23.38	0.98	87.92	107.75
LAUCI	118.23	120.52	0.98	94.42	101.92
LAUCT	108.45	109.95	0.99	94.72	102.73
LCMAX	22.37	22.47	1.00	89.16	111.16

3. AUCT/AUCI ratios

The AUCT/AUCI ratios were summarized in Table V-A-4.

Table V-A-4. AUCT/AUCI Ratios

Analysis Variable : AUCRATIO

TRT=1

N	Mean	Std Dev	Minimum	Maximum
24	0.92	0.03	0.81	0.97

TRT=2

N	Mean	Std Dev	Minimum	Maximum
23	0.91	0.05	0.76	0.96

B. Study under Nonfasting Conditions

Subjects: 18 subjects were enrolled in the study and all subjects completed the crossover. Data from 18 subjects (Subjects #1-18) were used in the pharmacokinetic/statistical evaluation per protocol.

Medical events: A total of 6 medical events (1 under treatment 1, 2 under treatment 2 and 3 for treatment 3.) were reported. No serious medical events were reported during the study.

Evaluation of study data: Reviewer recalculated all the pharmacokinetic parameters and statistics and the results of the recalculation are in agreement with the sponsor's submission.

1. Mean plasma etodolac levels

Mean plasma etodolac levels for the test and reference products under nonfasting conditions (treatments 2 and 3) were comparable to each other as shown in Table V-B-1 and Fig. P-2. Peak mean plasma levels for the test and reference products under nonfasting conditions were 9.20 mcg/mL and 9.24 mcg/mL, respectively, both occurring at 4.5 hours post-dose. The food effect is clearly shown: The peak mean etodolac concentration is approximately 30% lower under nonfasting conditions and the time to peak mean concentration is 4.5 hours under nonfasting conditions as compared to the 1.5 hours under fasting conditions.

TABLE V-B-1. MEAN PLASMA Etodolac LEVELS FOR TEST AND REFERENCE PRODUCTS UNDER FASTING/NONFASTING CONDITIONS
UNIT: PLASMA LEVEL=MCG/ML TIME=HRS
MEAN1=TEST-FAST; MEAN2=TEST-FOOD; MEAN3=REF-FOOD; RMEAN23=MEAN2/MEAN3 RATIO
SD=STANDARD DEVIATION
Test Lot #960645; Ref Lot #3950568

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	4.70	4.71	0.04	0.18	0.82	2.94
1	11.94	7.22	0.66	0.89	1.21	2.61
1.5	12.77	6.57	2.04	2.43	2.71	2.66
2	11.85	3.67	4.28	3.98	4.99	2.95
2.5	10.46	2.37	6.05	3.69	6.44	2.88
3	9.57	2.63	7.27	3.31	7.09	2.70
3.5	8.21	1.88	8.07	2.59	8.42	2.54
4	6.95	1.49	8.96	2.17	8.99	2.81
4.5	6.46	1.75	9.20	2.59	9.24	2.49
5	5.06	1.30	7.97	1.97	8.20	2.25
5.5	4.11	1.11	7.14	1.91	7.26	2.13
6	3.63	0.98	6.84	1.77	6.56	1.90
8	2.72	0.83	4.19	1.67	3.99	1.14
10	2.16	0.79	3.09	1.11	3.03	0.99
12	1.90	0.75	2.49	0.91	2.57	0.88
16	1.10	0.54	1.47	0.73	1.58	0.81
24	0.27	0.41	0.64	0.62	0.53	0.47
30	0.08	0.25	0.11	0.26	0.10	0.24

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.5	111.36	5.76	0.05
1	18.21	9.88	0.54
1.5	6.26	4.71	0.75
2	2.77	2.38	0.86
2.5	1.73	1.62	0.94
3	1.32	1.35	1.03
3.5	1.02	0.97	0.96
4	0.78	0.77	1.00
4.5	0.70	0.70	1.00
5	0.63	0.62	0.97
5.5	0.58	0.57	0.98
6	0.53	0.55	1.04
8	0.65	0.68	1.05
10	0.70	0.71	1.02
12	0.76	0.74	0.97
16	0.75	0.70	0.93
24	0.42	0.50	1.21
30	0.75	0.78	1.04

2. PK parameters and test/reference ratios

The arithmetic and geometric means for the PK parameters are shown in Table V-B-2. PK parameters, AUCT, AUCI, CMAX, LAUCT, LAUCI, and LCMAX for the test and reference products under nonfasting conditions are comparable to each other. Their

Test/Reference ratios range 0.97-1.07.

Table V-B-3 shows the LSMEANS and its test/reference ratios for the test and reference products under nonfasting conditions. The test/reference ratios for AUCT, AUCI, CMAX and log-transformed AUCT, AUCI and CMAX are within 0.98-1.07 and meet our acceptance criterion.

No sequence effect was observed for LAUCT, LAUCI AND LCMAX.

TABLE V-B-2. ARITHMETIC/GEOMETRIC MEANS AND RATIOS
UNDER FASTING/NONFASTING CONDITIONS
UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
MEAN1=TEST-FAST; MEAN2=TEST-FOOD; MEAN3=REF-FOOD; RMEAN23=MEAN2/MEAN3 RATIO
SD=STANDARD DEVIATION

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	79.46	22.44	79.23	21.32	81.28	21.83
AUCT	72.01	20.08	72.79	20.16	73.69	20.68
CMAX	17.47	3.33	10.60	2.12	10.07	2.53
KE	0.12	0.04	0.13	0.04	0.13	0.04
LAUCI	76.47	0.29	76.29	0.29	78.41	0.28
LAUCT	69.41	0.28	69.92	0.30	70.91	0.29
LCMAX	17.15	0.20	10.40	0.20	9.72	0.29
THALF	6.03	1.90	5.84	1.66	5.77	1.74
TMAX	1.59	0.73	3.95	1.48	4.11	2.27

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.00	0.98	0.97
AUCT	0.99	0.98	0.99
CMAX	1.65	1.73	1.05
KE	0.96	0.95	0.98
LAUCI	1.00	0.98	0.97
LAUCT	0.99	0.98	0.99
LCMAX	1.65	1.76	1.07
THALF	1.03	1.04	1.01
TMAX	0.40	0.39	0.96

TABLE V-B-3. LSMEANS AND TEST/REF RATIOS
UNDER FASTING/NONFASTING CONDITIONS
UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
LSM1=TEST-FAST; LSM2=TEST-FOOD; LSM3=REF-FOOD; RLSM23=LSM2/LSM3 RATIO

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	79.46	79.23	80.47	1.00	0.99	0.98
AUCT	72.01	72.79	73.69	0.99	0.98	0.99
CMAX	17.47	10.60	10.07	1.65	1.73	1.05
LAUCI	76.47	76.29	77.66	1.00	0.98	0.98
LAUCT	69.41	69.92	70.91	0.99	0.98	0.99
LCMAX	17.15	10.40	9.72	1.65	1.76	1.07

3. AUCT/AUCI ratios

Table V-B-4 shows the AUCT/AUCI ratios.

Table V-B-4. AUCT/AUCI RATIOS

Analysis Variable : AUCRATIO

TRT=1

N	Mean	Std Dev	Minimum	Maximum
18	0.91	0.03	0.85	0.96

TRT=2

N	Mean	Std Dev	Minimum	Maximum
18	0.92	0.02	0.87	0.95

TRT=3

N	Mean	Std Dev	Minimum	Maximum
17	0.91	0.03	0.86	0.95

VI. Formulation and Dissolution Data

1. Formulation

The test formulations for the 200 mg and 300 mg strengths capsules are shown in Table VI-1. The inactive ingredients of the test products are proportional in quantity between the 200 mg and 300 mg strengths. The inactive ingredients of the reference product are cellulose, lactose, povidone, sodium lauryl sulfate, sodium starch glycolate, and magnesium stearate.

Table VI-1. Test Formulation
Unit: mg/capsule

Ingredient	200 mg capsule	300 mg capsule
Etodolac, Micronized	200	300
Microcrystalline Cellulose, NF		
Povidone USP		
Colloidal Silicon Dioxide, NF		
Lactose Monohydrate		
Magnesium Stearate, NF		

2. Assay and content uniformity data

Table VI-2 shows the assay and content uniformity for the test and reference products.

Table VI-2. Assay and Content Uniformity

Product	Assay, %	Content Uniformity, % (%CV)
Test: Etodolac Capsules, 200 mg Lot #780005 Lot size: apsules	96.7	95.0-98.6
Reference: Lodine[R], 200 mg Lot #3950567 Exp:	100	-
Test: Etodolac Capsules, 300 mg Lot #960645 Lot size: capsules	99.1	96.6-100.2
Reference: Lodine[R], 300 mg Lot #3950568 Exp: 3/98	97	96.3-98.1

3. Dissolution testing

FDA dissolution method was used. The test and reference products met the FDA specifications as shown in Table VI-3. The FDA dissolution specifications are shown below:

Medium and Volume	0.1 M phosphate buffer, pH 7.5; 1000 mL
Apparatus and rpm	1 (basket); 100 rpm
Time	30 min
Tolerances	NLT (Q)

However, there were discrepancies found in the dissolution tables the firm submitted. Tables on pages 1914-1915 show sampling intervals of 5, 10, 20 and 30 minutes and tables on pages 1919-1921 show sampling intervals of 5, 10, 15, and 30 minutes. The firm confirmed that sampling intervals of 5, 10, 20 and 30 minutes are correct by FAX amendment dated 6/17/97.

VII. Summary and Comments

1. **Pharmacokinetic and statistical evaluation:**

   A. Study under fasting conditions: Mean plasma etodolac levels for the test and reference products under fasting conditions were comparable. The LSMEANS for the PK parameters are comparable for the test and reference products and the 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within the acceptable range of 80-125%.

   B. Study under nonfasting conditions: The food effect is clearly shown: The peak mean etodolac concentration is approximately 30% lower under nonfasting conditions and the time to peak mean concentration is 4.5 hours under nonfasting conditions as compared to the 1.5 hours under fasting conditions. Mean plasma etodolac levels for the test and reference products under nonfasting conditions (treatments 2 and 3) were comparable. The test/reference ratios for LSMEANS of AUCT, AUCI, CMAX and log-transformed AUCT, AUCI and CMAX are within 0.98-1.07.

2. **Bioanalytical method validation:** Pre-study and within-study validation data are acceptable for the fasting and nonfasting studies.

3. **Dissolution testing:** The test products, 200 mg and 300 mg strengths, met the FDA dissolution specifications.

4. **Drug products:** The assay and content uniformity data for the test and reference products are acceptable. The batch size of the test product was capsules. The inactive ingredients of the test products are proportional in quantity between the 200 mg and 300 mg strengths.

5. **Medical events:** No serious medical events were reported during the two studies under fasting and nonfasting studies.

6. **Waiver:** Waiver on 200 mg capsules is granted.

VIII. Deficiency

None.

IX. Recommendations

1. The two *in vivo* bioequivalence studies conducted under fasting and nonfasting conditions by Taro on its Etodolac Capsules, 300 mg strength, lot #960645, comparing it to Wyeth-Ayerst's Lodine®, 300 mg capsules, lot #3950568, have been found acceptable. The studies demonstrate that Taro's Etodolac Capsules, 300 mg strength, is bioequivalent to the reference product, Wyeth-Ayerst's Lodine®, 300 mg capsules.

2. The FDA dissolution testing conducted by Taro on its Etodolac Capsules, 300 mg strength, lot #960645, and 200 mg strength, lot #780005, is acceptable.

3. The FDA dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.1 M phosphate buffer, pH 7.5, at 37°C using USP 23 Apparatus 1 (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the recommendations.

Moo Park, Ph.D.
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6/30/97

Concur: _____ Date: 9/14/97

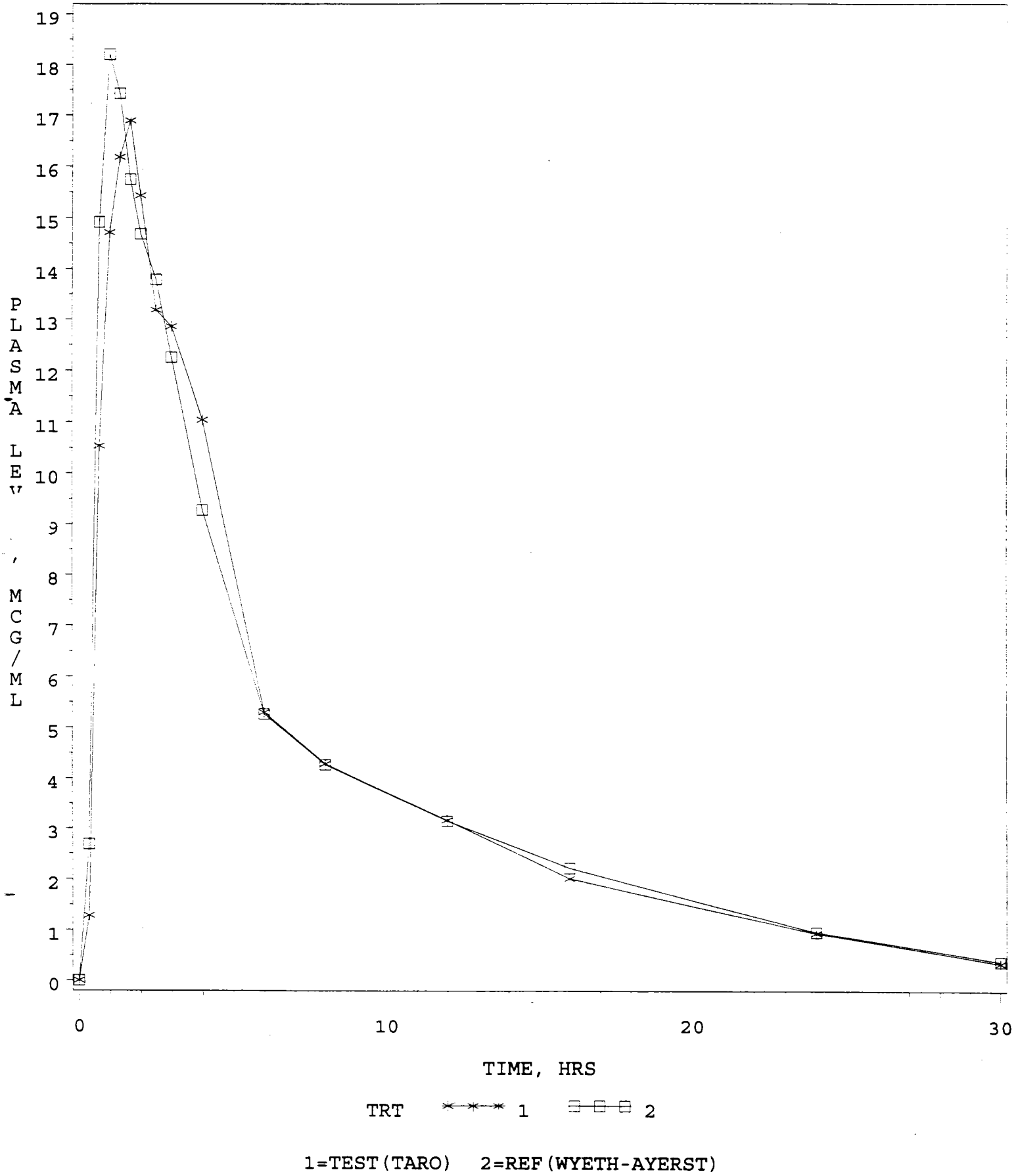
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

Table VI-3. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product(Generic Name)	Etodolac Capsules					
Strength	200 and 300 mg					
ANDA Number	75078					
Applicant	Taro					
Reference Drug Product	Wyeth-Ayerst's Lodine^{R} Capsules					
II. USP Method for Dissolution Testing						
Medium and Volume	Phosphate buffer, pH 7.5; 1000 mL					
Apparatus and rpm	1(basket); 100 rpm					
Time	30 min					
Tolerances	NLT (Q)					
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No: 780005 Strength: 200 mg No of Units: 12			Reference Product Lot No: 3950567 Strength: 200 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
5	45.7		43.5	46.6		21.4
10	72.7		20.2	85.4		7.7
20	94.3		6.1	98.7		1.3
30	97.8		1.7	100		1.2
Time	Test Product Lot No: 960645 Strength: 300 mg No of Units: 12			Reference Product Lot No: 3950568 Strength: 300 mg No of Units: 12		

Min	Mean	Range	%CV	Mean	Range	%CV
5	35.8		27.5	26.1		35
10	70.3		18.4	82.8		7.3
20	90.3		7.2	98.6		1.2
30	95.9		1.9	100.7		0.9

FIG P-/. PLASMA ETODOLAC LEVELS

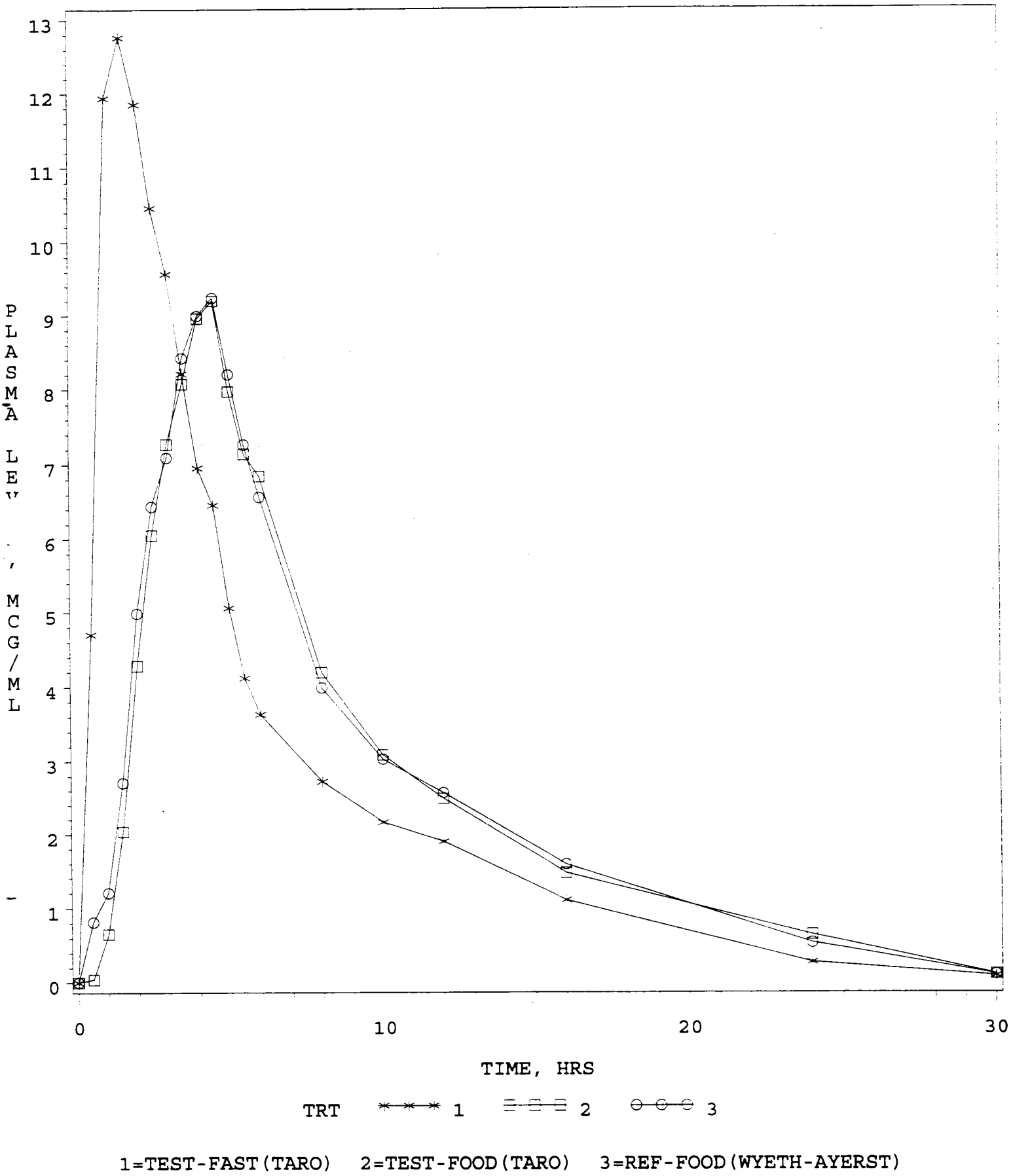
ETODOLAC CAPSULES, 300 MG, ANDA #75-078
UNDER FASTING CONDITIONS
DOSE=1 X 300 MG



1=TEST(TARO) 2=REF(WYETH-AYERST)

FIG P-2. PLASMA ETODOLAC LEVELS

ETODOLAC CAPSULES, 300 MG, ANDA #75-078
UNDER NONFASTING CONDITIONS
DOSE=1 X 300 MG



1=TEST-FAST(TARO) 2=TEST-FOOD(TARO) 3=REF-FOOD(WYETH-AYERST)