CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-492

Approval Letter

ANDA 75-492 FEB 11 2000

Keller & Heckman
Attention: John Dubeck
U.S. Agent for: Biovail Laboratories Incorporated
1001 G Street N.W., Suite 500 West
Washington D.C. 20001

Dear Sir:

This is in reference to your abbreviated new drug application dated October 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diclofenac Sodium Extended-Release Tablets, 100 mg.

Reference is also made to your amendment dated November 19, 1999.

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 Diclofenac Sodium Extended-Release Tablets, 100 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Voltaren®-XR Tablets, 100 mg of Novartis Pharmaceutical Corporation).

We acknowledge that the following "interim" dissolution testing has been incorporated into your manufacturing controls and stability program. The "interim" dissolution test and tolerances are:

The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.5, at 37°C using USP Apparatus II(paddle) at 50 rpm. The test product should meet the following interim specifications:

Time (hours)	% Dissolved
1	NMT 25%
4	30 - 50%
8	50 - 75%
16	NLT 85%

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. The supplemental application should be submitted as "Supplement-Changes Being Effected" when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplement should be submitted as a "Prior Approval Supplement".

Under section 506 A of the Act, 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 that 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-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.

Sincerely yours,

/S/

Janet Woodcock, M.D. FEB 11 2000
Director
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-492

FINAL PRINTED LABELING

Diclofenac Sodium Extended-release Tablets, 100 mg in Bottles of 1000

NDC 0093-1041-10

DICLOFENAC
SODIUM
Extended-release
Tablets
100 mg

Each tablet contains:
Diclofenac Sodium 100 mg

℞ only

1000 TABLETS

TEVA

Dosage: See package insert.
Do not store above 30°C (86°F).
Protect from moisture.
PHARMACIST: Container closure is not child resistant.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Manufactured by:
Biovail Corporation International
Manufacturing Division
Steinbach, Manitoba
Canada R0A 2T3

LL-0182-00/Iss. 5/99

Printed in U.S.A.

FEB 11 20

0093-1041-10

NDC 0093-1041-10

DICLOFENAC
SODIUM
Extended-release
Tablets
100 mg

Each tablet contains:
Diclofenac Sodium 100 mg

℞ only

1000 TABLETS

TEVA

Dosage: See package insert.
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LL-0182-00/Iss. 5/99

Printed in U.S.A.

FEB 11 200

0093-1041-10

Diclofenac Sodium Extended-release Tablets, 100 mg in Bottles of 500

NDC 0093-1041-05

DICLOFENAC SODIUM Extended-release Tablets **100 mg**

Each tablet contains:
Diclofenac Sodium 100 mg

℞ only

TEVA

Dosage: See package insert.
Do not store above 30°C (86°F).
Protect from moisture.
PHARMACIST: Container closure is not child resistant.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Manufactured by:
Biovail Corporation International
Manufacturing Division
Steinbach, Manitoba
Canada R0A 2T3

LL-0183-00/Iss. 5/99

N 3 0093-1041-05 0

Printed in U.S.A.

FEB 11 2000

NDC 0093-1041-05

DICLOFENAC SODIUM Extended-release Tablets **100 mg**

Each tablet contains:
Diclofenac Sodium 100 mg

℞ only

TEVA

Dosage: See package insert.
Do not store above 30°C (86°F).
Protect from moisture.
PHARMACIST: Container closure is not child resistant.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured for:
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Sellersville, PA 18960

Manufactured by:
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Manufacturing Division
Steinbach, Manitoba
Canada R0A 2T3

LL-0183-00/Iss. 5/99

N 3 0093-1041-05 0

Printed in U.S.A.

FEB 11 2000

NDC 0093-1041-01

DICLOFENAC SODIUM Extended-release Tablets 100 mg

Each tablet contains:
Diclofenac Sodium 100 mg

℞ only

TEVA

Usage: See package insert.
Do not store above 30°C (86°F).
Protect from moisture.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Manufactured by:
Biovail Corporation International
Manufacturing Division
Steinbach, Manitoba
Canada R0A 2T3

LL-0181-00/Iss. 5/99

0093-1041-01

Printed in U.S.A.

8 11 2000

of certain drugs. Ingestion of diclofenac may increase serum concentrations of digoxin and methotrexate and increase cyclosporine's nephrotoxicity. Patients who begin taking diclofenac or who increase their diclofenac dose or any other NSAID while taking digoxin, methotrexate, or cyclosporine may develop toxicity characteristics for these drugs. They should be observed closely, particularly if renal function is impaired. In the case of digoxin, serum levels should be monitored.

Lithium: Diclofenac decreases lithium renal clearance and increases lithium plasma levels. In patients taking diclofenac and lithium concomitantly, lithium toxicity may develop.

Oral Hypoglycemics: Diclofenac does not alter glucose metabolism in normal subjects nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experiences, of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac that necessitated changes in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Diuretics: Diclofenac and other NSAIDs can inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other Drugs: In small groups of patients (7-10/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline, or digitoxin did not significantly affect the peak levels and AUC values of diclofenac. Phenobarbital toxicity has been reported to have occurred in a patient on chronic phenobarbital treatment following the initiation of diclofenac therapy.

Protein Binding

In vitro, diclofenac interferes minimally or not at all with the protein binding of salicylic acid (20% decrease in binding), tolbutamide, prednisolone (10% decrease in binding), or warfarin. Benzylpenicillin, ampicillin, oxacillin, chlrotetracycline, doxycycline, cephalothin, erythrommycin, and sulfamethoxazole have no influence *in vitro* on the protein binding of diclofenac in human serum.

Drug/Laboratory Test Interactions

Effect on Blood Coagulation: Diclofenac increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, however, and are unlikely to be clinically important. Diclofenac is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day (or 12 mg/m²/day, approximately the human dose) have revealed no significant increases in tumor incidence. There was a slight increase in benign mammary fibroadenomas in mid-dose-treated (0.5 mg/kg/day or 3 mg/m²/day) female rats (high-dose females had excessive mortality), but the increase was not significant for this common rat tumor. A 2-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/kg/day (0.9 mg/m²/day) in males and 1 mg/kg/day (3 mg/m²/day) in females did not reveal any oncogenic potential. Diclofenac sodium did not show mutagenic activity in *in vitro* point mutation assays in mammalian (mouse lymphoma) and microbial (yeast, Ames) test systems and was nonmutagenic in several mammalian *in vitro* and *in vivo* tests, including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. Diclofenac sodium administered to male and female rats at 4 mg/kg/day (24 mg/m²/day) did not affect fertility.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Reproduction studies have been performed in mice given diclofenac sodium (up to 20 mg/kg/day or 60 mg/m²/day) and in rats and rabbits given diclofenac sodium (up to 10 mg/kg/day or 60 mg/m²/day for rats, and 60 mg/m²/day for rabbits), and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Diclofenac has been shown to cross the placental barrier in mice and rats. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless the benefits to the mother justify the potential risk to the fetus. Because of the risk to the fetus resulting in premature closure of the ductus arteriosus, diclofenac should be avoided in late pregnancy.

Labor and Delivery

The effects of diclofenac on labor and delivery in pregnant women are unknown. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of diclofenac during late pregnancy should be avoided and, as with other nonsteroidal anti-inflammatory drugs, it is possible that diclofenac may inhibit uterine contractions and delay parturition.

Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants from diclofenac, 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 of diclofenac in pediatric patients have not been established.

Geriatric Use

Of the more than 6000 patients treated with diclofenac in U.S. trials, 31% were older than 65 years of age. No overall difference was observed between efficacy, adverse event, or pharmacokinetic profiles of older and younger patients. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

ADVERSE REACTIONS

Adverse reaction information is derived from blinded, controlled, and open-label clinical trials, as well as worldwide marketing experience. In the description below, rates of more common events represent clinical study results; rarer events are derived principally from marketing experience and publications, and accurate rate estimates are generally not possible.

The following adverse reactions were reported in patients treated with diclofenac:

Incidence Greater Than 1% - Causal Relationship Probable:
(All derived from clinical trials.)
*Incidence, 3% to 9% (incidence of unmarked reactions is 1%-3%).

Body as a Whole: Abdominal pain or cramps, *headache, *fluid retention, abdominal distention.

Digestive: Diarrhea, *indigestion, *nausea, *constipation, *flatulence, liver test abnormalities, *PUB, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer (see above and also WARNINGS).

Nervous System: Dizziness.

Skin and Appendages: Rash, pruritus.

Special Senses: Tinnitus.

Incidence Less Than 1% - Causal Relationship Probable:

Conjugates of unchanged diclofenac account for 5%-10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. Conjugates of the principal metabolite account for 20%-30% of the dose excreted in the urine and for 10%-20% of the dose excreted in the bile. Conjugates of three other metabolites together account for 10%-20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

Special Populations: *Geriatric Population:* An 8-day study, comparing the kinetics of diclofenac (100 mg diclofenac sodium extended-release tablets q.d.) in osteoarthritis patients older than 65 years versus younger than 65 years showed no significant differences between the two groups with respect to peak plasma levels, time to peak levels, or AUC.

Patients with Renal and/or Hepatic Impairment: To date, no differences in the pharmacokinetics of diclofenac have been detected in studies of patients with renal (50 mg intravenously) or hepatic impairment (100 mg oral solution). In patients with renal impairment (N=5, creatinine clearance 3 to 42 mL/min), AUC values and elimination rates were comparable to those in healthy subjects. In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubins, N=10), diclofenac concentrations and urinary elimination values were comparable to those in healthy subjects.

Clinical Studies: *Diclofenac-Sodium Extended-release Tablets in Osteoarthritis:* The use of diclofenac sodium extended-release tablets in controlling the signs and symptoms of osteoarthritis was assessed in two double-blind, controlled trials in which 742 patients participated and 517 patients were treated for 3 months. In one active- and placebo-controlled study, diclofenac sodium extended-release tablets at doses of 100 mg q.d. were comparable to diclofenac sodium enteric coated tablets 50 mg b.i.d. in patients whose osteoarthritis symptoms were stabilized after 2 weeks of treatment with diclofenac sodium enteric coated tablets 75 mg b.i.d. In another study, diclofenac sodium extended-release tablets at doses of 100 mg q.d. and 100 mg b.i.d. were compared to diclofenac sodium enteric coated tablets 50 mg q.i.d. Diclofenac sodium extended-release tablets 100 mg b.i.d. were comparable to diclofenac sodium enteric coated tablets 50 mg q.i.d. With the diclofenac sodium extended-release tablet formulation, although there was a trend toward greater efficacy at doses of 200 mg daily than 100 mg daily, there was also an increase in side effects when 200 mg of diclofenac sodium extended-release tablets were administered to patients with osteoarthritis.

Diclofenac-Sodium Extended-release Tablets in Rheumatoid Arthritis: The use of diclofenac sodium extended-release tablets in controlling the signs and symptoms of rheumatoid arthritis was assessed in two double-blind, controlled trials in which 704 patients participated and 441 patients were treated for 3 months. In one active- and placebo-controlled study, diclofenac sodium extended-release tablets 100 mg q.d. were comparable to diclofenac sodium enteric coated tablets 50 mg b.i.d. in patients whose rheumatoid arthritis symptoms were stabilized after 2 weeks' treatment of diclofenac sodium enteric coated tablets 75 mg b.i.d. In another study, diclofenac sodium extended-release tablets at doses of 100 mg q.d. and 100 mg b.i.d. were compared to diclofenac sodium enteric coated tablets 50 mg q.i.d. Diclofenac sodium extended-release tablets 100 mg b.i.d. were comparable to diclofenac sodium enteric coated tablets 50 mg q.i.d. There was a trend toward greater efficacy with doses of 200 mg daily as compared to 100 mg daily of diclofenac sodium extended-release tablets. There was also an increase in side effects when 200 mg of diclofenac's sodium extended-release tablets were administered to patients with rheumatoid arthritis.

INDIVIDUALIZATION OF DOSAGE:

Diclofenac, like other NSAIDs, shows interindividual differences in both pharmacokinetics and clinical response (pharmacodynamics). Consequently, the recommended strategy for initiating therapy is to use a starting dose likely to be effective for the majority of patients and to adjust dosage thereafter based on observation of diclofenac's beneficial and adverse effects.

In patients weighing less than 60 kg (132 lb), or where the severity of the disease, concomitant medication, or other diseases warrant, the maximum recommended total daily dose of Diclofenac Sodium Extended-release Tablets should be reduced. Experience with other NSAIDs has shown that starting therapy with maximum doses in patients at increased risk due to renal or hepatic disease, low body weight (<60 kg), advanced age, a known ulcer diathesis, or known sensitivity to NSAID effects, is likely to increase frequency of adverse reactions and is not recommended (see PRECAUTIONS).

Osteoarthritis/Rheumatoid Arthritis: For patients with osteoarthritis, the usual starting dose of Diclofenac Sodium Extended-release Tablets is 100 mg q.d.

For most patients with rheumatoid arthritis, the usual starting dose of Diclofenac Sodium Extended-release Tablets is 100 mg q.d. Patients requiring more relief of pain and inflammation may increase the dose to 200 mg/day. In clinical trials, patients receiving 200 mg/day were less likely to drop from the trial due to lack of efficacy than patients receiving 100 mg/day. Dosages above 225 mg/day are not recommended in patients with rheumatoid arthritis because of increased risk of adverse events.

INDICATIONS AND USAGE:

Diclofenac Sodium Extended-release tablets are indicated for chronic therapy of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS:

Diclofenac Sodium Extended-release Tablets is contraindicated in patients with known hypersensitivity to diclofenac and diclofenac-containing products. Diclofenac 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 diclofenac have been reported in such patients (see WARNINGS-Anaphylactoid Reactions, and PRECAUTIONS-Preexisting Asthma).

WARNINGS:

Gastrointestinal Effects: Peptic ulceration and gastrointestinal bleeding have been reported in patients receiving diclofenac. Physicians and patients should therefore remain alert for ulceration and bleeding in patients treated chronically with diclofenac even in the absence of previous G.I. tract symptoms. It is recommended that patients be maintained on the lowest dose of diclofenac possible, consistent with achieving a satisfactory therapeutic response.

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

Diclofenac Sodium Extended-release Tablets

Rx only

Prescribing in

DESCRIPTION:

Diclofenac sodium is a benzeneacetic acid derivative, designated chemically as 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt. The structural formula is shown in Figure 1.

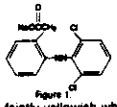

Figure 1.

Diclofenac sodium is a faintly yellowish white to light beige virtually odorless, slightly hygroscopic crystalline powder. The molecular weight of diclofenac sodium is 318.14. It is freely soluble in methanol, soluble in ethanol, and practically insoluble in chloroform and in dilute acid. Diclofenac sodium is sparingly soluble in water. The n-octanol/water partition coefficient is 13.4 at pH 7.4 and 1545 at pH 5.2. This salt has a dissociation constant (pKa) of 4.0 ± 0.2 at 25°C in water.

Diclofenac sodium is available as Diclofenac Sodium Extended-release Tablets of 100 mg for oral administration.

Diclofenac Sodium Extended-release Tablets Inactive Ingredients: hydroxyethyl cellulose, isopropyl alcohol, anhydrous lactose, magnesium stearate, opadry II (pink), opadry (clear), povidone (K90), colloidal silicone dioxide, talc.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: Diclofenac, the anion in Diclofenac Sodium Extended-release Tablets, is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity, as well as contribute to its efficacy in relieving pain related to inflammation and primary dysmenorrhea. With regard to its analgesic effect, diclofenac is not a narcotic.

Pharmacokinetics: Diclofenac Sodium Extended-release Tablets contain the therapeutic moiety, diclofenac. Diclofenac Sodium Extended-release Tablets are formulated to release drug over a prolonged period. The pattern of drug release and absorption is described below and is shown in Table 1.

Table 1
Mean (% CV) Pharmacokinetics of Diclofenac Following Single Oral Doses of Diclofenac Sodium Extended-release Tablets

Drug	Dose (mg)	AUC (ng-hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
Diclofenac Sodium	100	2750.19 (20.21%)	423.58 (26.59%)	3.98 (70.45%)

Absorption: Under fasting conditions, diclofenac is completely absorbed from the gastrointestinal tract. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available.

Diclofenac Sodium Extended-release Tablets: The extent of diclofenac absorption from the extended-release tablet is not significantly affected when the drug is taken with food, however, food significantly altered the absorption pattern as indicated by a delay of 1 to 2 hours in T_{max} and a two-fold increase in C_{max} values. The plasma profile of the extended-release tablet, under fasting conditions, was characterized by multiple peaks and high intersubject variability in blood profiles. In contrast, the plasma profile for the extended-release tablets under fed conditions showed a more consistent absorption pattern with a single peak usually occurring between 5 and 6 hours after the meal.

Distribution: Plasma concentrations of diclofenac decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of distribution are about 350 mL/min and 550 mL/kg, respectively. More than 99% of diclofenac is reversibly bound to human plasma albumin.

As with other NSAIDs, diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism and Elimination: Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile.

Conjugates of unchanged diclofenac account for 5%-10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. Conjugates of the principal metabolite account for 20%-30% of the dose excreted in the urine and for 10%-20% of the dose excreted in the bile. Conjugates of three other metabolites together account for 10%-20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

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WARNINGS:

Gastrointestinal Effects: Peptic ulceration and gastrointestinal bleeding have been reported in patients receiving diclofenac. Physicians and patients should therefore remain alert for ulceration and bleeding in patients treated chronically with diclofenac even in the absence of previous G.I. tract symptoms. It is recommended that patients be maintained on the lowest dose of diclofenac possible, consistent with achieving a satisfactory therapeutic response.

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

Hepatic Effects: Elevations of one or more liver tests may occur during diclofenac therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e., less than 3 times the ULN [=the Upper Limit of the Normal range]), or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the hepatic enzymes, ALT (SGPT) is the one recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5700 patients at some time during diclofenac sodium treatment. In a large, open, controlled trial, meaningful elevations of ALT and/or AST occurred in about 4% of 3700 patients treated for 2-6 months, including marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDS. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (see ADVERSE REACTIONS).

In addition to enzyme elevations seen in clinical trials, postmarketing surveillance has found rare cases of severe hepatic reactions, including liver necrosis, jaundice, and fulminant fatal hepatitis with and without jaundice. Some of these rare reported cases underwent liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label) that involved 3700 patients monitored first at 8 weeks and 1200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with diclofenac. Postmarketing experience has shown severe hepatic reactions can occur at any time during treatment with diclofenac. Cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first two months of therapy. Based on these experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac (see PRECAUTIONS-Laboratory Tests). As with other NSAIDs, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), diclofenac should be discontinued immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

Anaphylactoid Reactions: As with other NSAIDs anaphylactoid reactions may occur in patients without prior exposure to diclofenac. Diclofenac 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-Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease: In cases with advanced kidney disease, treatment with diclofenac, as with other NSAIDs, should only be initiated with close monitoring of the patient's kidney functions (see PRECAUTIONS-Renal Effects).

Pregnancy: In late pregnancy, diclofenac should, as with other NSAIDs, be avoided because it will cause premature closure of the ductus arteriosus (see PRECAUTIONS - Pregnancy, Teratogenic Effects, Pregnancy Category B, and Labor and Delivery).

PRECAUTIONS:

General: Diclofenac Sodium Extended-release Tablets should not be used concomitantly with other diclofenac-containing products since they also circulate in plasma as the diclofenac anion.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking diclofenac. Therefore, as with other NSAIDs, diclofenac should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions

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Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking diclofenac. Therefore, as with other NSAIDs, diclofenac should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions predisposing to fluid retention.

Hematologic Effects: Anemia is sometimes seen in patients receiving diclofenac or other NSAIDs. This may be due to fluid retention, G.I. blood loss, or an incompletely described effect upon erythropoiesis.

Renal Effects: As a class, NSAIDs have been associated with renal papillary necrosis and other abnormal renal pathology in long-term administration to animals. In oral diclofenac studies in animals, some evidence of renal toxicity was noted. Isolated incidents of papillary necrosis were observed in a few animals at high doses (20-120 mg/kg) in several baboon subacute studies. In patients treated with diclofenac, rare cases of interstitial nephritis and papillary necrosis have been reported (see ADVERSE REACTIONS).

A second form of renal toxicity, generally associated with NSAIDs, is seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in a reduction of renal blood flow, which may precipitate overt renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Cases of significant renal failure in patients receiving diclofenac have been reported from marketing experience, but were not observed in over 4000 patients in clinical trials during which

serum creatinine and BUN values were followed serially. There were only 11 patients (0.3%) whose serum creatinine and current serum BUN values were greater than 2.0 mg/dL and 40 mg/dL, respectively, while on diclofenac (mean rise in the 11 patients: creatinine 2.3 mg/dL and BUN 28.4 mg/dL).

Since diclofenac metabolites are eliminated primarily by the kidneys, patients with significantly impaired renal function should be more closely monitored than subjects with normal renal function.

Porphyria: The use of diclofenac in patients with hepatic porphyria should be avoided. To date, 1 patient has been described in whom diclofenac probably triggered a clinical attack of porphyria. The postulated mechanism, demonstrated in rats, for causing such attacks by diclofenac, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA).

Aseptic Meningitis: As with other NSAIDs, aseptic meningitis with fever and coma has been observed on rare occasions in patients on diclofenac therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on diclofenac, the possibility of its being related to diclofenac should be considered.

Pre-existing Asthma: About 10% of patients with asthma may have aspirin- sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma 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, diclofenac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with preexisting asthma.

Other Precautions: The pharmacologic activity of diclofenac may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting underlying conditions.

In order to avoid exacerbation of manifestations of adrenal insufficiency, patients who have been on prolonged corticosteroid treatment should have their therapy tapered slowly rather than discontinued abruptly when diclofenac is added to the treatment program.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving diclofenac, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Information for Patients:

Diclofenac, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, and more rarely, liver toxicity (see WARNINGS, Hepatic Effects), which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis and have a major role in the management of pain, but they also may 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 NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Because serious G.I. 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, Gastrointestinal Effects, *Risk of G.I. Ulcerations, Bleeding, and Perforation with NSAID Therapy*). If diclofenac is used chronically, patients should also be instructed to report any signs and symptoms that might be due to hepatotoxicity of diclofenac; these symptoms may become evident between visits when periodic liver laboratory tests are performed (see WARNINGS, Hepatic Effects, and PRECAUTIONS-Laboratory Tests).

Laboratory Tests

Hepatic Effects: Transaminases and other hepatic enzymes should be monitored in patients treated with NSAIDs. For patients on diclofenac therapy, it is recommended that a determination be made within 4 weeks of initiating therapy and at intervals thereafter. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.) and abnormal liver tests are detected, persist or worsen, diclofenac should be discontinued immediately.

Hematologic Effects: Patients on long-term treatment with NSAIDs, including diclofenac, 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.

Drug Interactions

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

Anticoagulants: While studies have not shown diclofenac to interact with anticoagulants of the warfarin type, caution should be exercised, nonetheless, since interactions have been seen with other NSAIDs. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function as well, concurrent therapy with all NSAIDs, including diclofenac, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

Digoxin, Methotrexate, Cyclosporine: Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of diclofenac may increase serum concentrations of digoxin and methotrexate and increase cyclosporine's nephrotoxicity. Patients who begin taking diclofenac or who increase their diclofenac dose or any other NSAID while taking digoxin, methotrexate, or cyclosporine may develop toxicity characteristics for these drugs. They should be observed closely, particularly if renal function is impaired. In the case of digoxin, serum levels should be monitored.

Lithium: Diclofenac decreases lithium renal clearance and increases lithium plasma levels. In patients taking diclofenac and lithium concomitantly, lithium toxicity may develop.

Oral Hypoglycemics: Diclofenac does not alter glucose metabolism in normal subjects nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experiences, of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac that necessitated changes in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Diuretics: Diclofenac and other NSAIDs can inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other Drugs: In small groups of patients (7-10/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline, or digitoxin did not significantly affect the peak levels and AUC values of diclofenac

elderly are likely to tolerate adverse reactions less well than younger patients.

ADVERSE REACTIONS

Adverse reaction information is derived from blinded, controlled, and open-label clinical trials, as well as worldwide marketing experience. In the description below, rates of more common events represent clinical study results; rarer events are derived principally from marketing experience and publications, and accurate rate estimates are generally not possible.

The following adverse reactions were reported in patients treated with diclofenac:

Incidence Greater Than 1% - Causal Relationship Probable:
(All derived from clinical trials.)
*Incidence, 3% to 9% (incidence of unmarked reactions is 1%-3%).

Body as a Whole: Abdominal pain or cramps, *headache, *fluid retention, abdominal distention.

Digestive: Diarrhea, *indigestion, *nausea, *constipation, *flatulence, liver test abnormalities, *PUB, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer (see above and also WARNINGS).

Nervous System: Dizziness.

Skin and Appendages: Rash, pruritus.

Special Senses: Tinnitus.

Incidence Less Than 1% - Causal Relationship Probable:
(Adverse reactions reported only in worldwide marketing experience or in the literature, not seen in clinical trials, are considered rare and are *italicized*).

Body as a Whole: Malaise, swelling of lips and tongue, photosensitivity, *anaphylaxis*, anaphylactoid reactions.

Cardiovascular: Hypertension, congestive heart failure.

Digestive: Vomiting, jaundice, melena, *esophageal lesions*, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, *hepatic necrosis, cirrhosis, hepatorenal syndrome*, appetite change, pancreatitis with or without concomitant hepatitis, *colitis*.

Hemic and Lymphatic: Hemoglobin decrease, leukopenia, thrombocytopenia, *eosinophilia, hemolytic anemia, aplastic anemia, agranulocytosis*, purpura, *allergic purpura*.

Metabolic and Nutritional Disorders:
Azotemia.

Nervous System: Insomnia, drowsiness, depression, diplopia, anxiety, irritability, *aseptic meningitis, convulsions*.

Respiratory: Epistaxis, asthma, laryngeal edema.

Skin and Appendages: Alopecia, urticaria, eczema, dermatitis, *bullous eruption, erythema multiforme major*, angioedema, *Stevens-Johnson syndrome*.

Special Senses: Blurred vision, taste disorder, reversible and irreversible hearing loss, scotoma.

Urogenital: *Nephrotic syndrome*, proteinuria, *oliguria, interstitial nephritis, papillary necrosis, acute renal failure*.

Incidence Less Than 1% - Causal Relationship Unknown:
(The following reactions have been reported in patients taking diclofenac under circumstances that do not permit a clear attribution of the reaction to diclofenac. These reactions are being included as alerting information to physicians. Adverse reactions reported only in worldwide marketing experience or in the literature, not seen in clinical trials, are considered rare and are *italicized*).

Body as a Whole: Chest pain.

Cardiovascular: Palpitations, *flushing*, tachycardia, premature ventricular contractions, myocardial infarction, *hypotension*.

Digestive: *Intestinal perforation*.

Hemic and Lymphatic: *Bruising*.

Metabolic and Nutritional Disorders: Hypoglycemia, *weight loss*.

Nervous System: Paresthesia, memory disturbance, nightmares, tremor, tic, *abnormal coordination, disorientation, psychotic reaction*.

Respiratory: Dyspnea, hyperventilation, edema of pharynx.

Skin and Appendages: Excess perspiration, *exfoliative dermatitis*.

Special Senses: Vitreous floaters, night blindness, amblyopia.

Urogenital: Urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.

OVERDOSAGE:

Worldwide reports of overdosage with diclofenac cover 66 cases. In approximately one-half of these reports of overdosage, concomitant medications were also taken. The highest dose of diclofenac was 5.0 g in a 17-year-old male who suffered loss of consciousness, increased intracranial pressure, aspiration pneumonitis, and died 2 days after overdose. The next highest doses of diclofenac were 4.0 g and 3.75 g. The 24-year-old female who took 4.0 g and the 28- and 42-year-old females, each of whom took 3.75 g did not develop any clinically significant signs or symptoms. However, there was a report of a 17-year-old female who experienced vomiting and drowsiness after an overdose of 2.37 g of diclofenac.

Animal LD_{50} values show a wide range of susceptibilities to acute overdosage, with primates being more resistant to acute toxicity than rodents (LD_{50} in mg/kg-rats, 55; dogs, 500; monkeys, 3200).

In case of acute overdosage, it is recommended that the stomach be emptied by vomiting or lavage. Forced diuresis may theoretically be beneficial because the drug is excreted in the urine. The effect of dialysis or hemoperfusion in the elimination of diclofenac (99% protein-bound; see CLINICAL PHARMACOLOGY) remains unproven. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption of diclofenac.

DOSAGE AND ADMINISTRATION

Diclofenac may be administered as 100mg Diclofenac Sodium Extended-release Tablets. Diclofenac Sodium Extended-release Tablets is not indicated for the management of acute painful conditions and should be used as chronic therapy in patients with osteoarthritis and rheumatoid arthritis.

The dosage of diclofenac should be individualized to the lowest effective dose to minimize adverse effects (see INDIVIDUALIZATION OF DOSAGE).

Osteoarthritis: The recommended dosage for chronic therapy with Diclofenac Sodium Extended-release Tablets is 100 mg q.d. Dosages of Diclofenac Sodium Extended-release Tablets of 200 mg daily are not recommended for patients with osteoarthritis. Dosages above 200 mg/day have not been studied in patients with osteoarthritis.

Rheumatoid Arthritis: The recommended dosage for chronic therapy with Diclofenac Sodium Extended-release tablets is 100 mg q.d. In the rare patient where Diclofenac Sodium Extended-release Tablets 100 mg/day is unsatisfactory, the dose may be increased to 100 mg b.i.d. if the benefits outweigh the clinical risks. Dosages above 225 mg/day are not recommended in patients with rheumatoid arthritis.

HOW SUPPLIED

Diclofenac Sodium Extended-release Tablets
100 mg - unscored, pink, round film coated tablets, engraved with "93" on one side and "1041" on the other side.

Metabolic and Nutritional Disorders: Hypoglycemia, *weight loss*

Nervous System: Paresthesia, memory disturbance, nightmares, tremor, tic, *abnormal coordination, disorientation, psychotic reaction*

Respiratory: Dyspnea, hyperventilation, edema of pharynx.

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Bottles of 100	NDC 0093-1041-01
Bottles of 500	NDC 0093-1041-05
Bottles of 1000	NDC 0093-1041-10

Do not store above 30°C (86°F). Protect from moisture. Dispense in tight container (USP).

Manufactured by:
Biovail Corporation International
Manufacturing Division
Steinbach, Manitoba
Canada R0A 2T3

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

LB-0007-00 / Iss. 5/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-492

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO. 3 **[First Generic Drug]**

2. ANDA # 75-492 **[Diclofenac Sodium Extended-release Tablets]**

3. NAME AND ADDRESS OF APPLICANT
   Bioavail Laboratories Inc.
   (a wholly owned subsidiary of Bioavil Corp. International)
   St. Michael, BH1, Barbados, West Indies

   U.S. Agent:
   Keller & Heckman (Attention: John Dubeck)
   1001 G Street N.W., Suite 500 West
   Washington D.C. 20001
   Telephone: (202) 434-4125
   FAX: (202) 434-4654

4. LEGAL BASIS FOR ANDA SUBMISSION: See CR #1

5. SUPPLEMENT(S): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME
   Diclofenac Sodium Extended-release Tablets

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

9. AMENDMENTS AND OTHER DATES:
   Bioavail:

10/30/98	ANDA submission (via overnight courier)
01/19/99	New Correspondence (bioequivalence issue)
06/01/99	Response to CMC NA letter (dated 05/04/99)
09/29/99	Response to labeling deficiencies.
11/19/99	*Response to CMC NA letter (dated 11/10/99)

   FDA:

11/27/98	Acknowledgment (accepted for filing on 11/02/98)
05/04/99	FAX (CMC and labeling deficiencies, Bio letter)
11/10/99	FAX (CMC deficiency letter)

10. PHARMACOLOGICAL CATEGORY
    For the treatment of chronic osteoarthritis and rheumatoid arthritis.

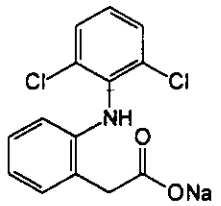
11. Rx or OTC Rx

12. RELATED IND/NDA/DMF(s) See CR #1

13. DOSAGE FORM Extended-Release oral tablets

14. POTENCY 100 mg

15. CHEMICAL NAME AND STRUCTURE
Generic name: Diclofenac Sodium
Chemical name: Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium (salt)
Formula: $C_{14}H_{10}Cl_2NNaO_2$, Molecular wt: 318.13 CAS registry number(s): 15307-86-5
Chemical structure:



16. RECORDS AND REPORTS: None

17. COMMENTS
The drug substance has a USP monograph (6th Supplement). The drug product is not listed in the USP 24.

Type II DMF of the bulk drug substance was reviewed in connection with this ANDA amendment, and was found adequate on 12/16/99.

Biovail's responses (dated 11/19/99) to the CMC deficiencies and their addendum to their 06/01/99 amendment were reviewed and found acceptable. There are no more CMC issues. Method validation request was issued on 10/25/99 to Northeast Regional Laboratory. NRL's method validation report (dated 01/11/00) indicated that Biovail's analytical method appears to be suitable for regulatory analysis of this product.

Labeling approval summary was signed off on 11/09/99.

Bioequivalence review was signed off on 03/04/99. The bio letter was faxed to the applicant on 05/04/99. There are no bioequivalence deficiencies. Biovail's accelerated stability data of the ANDA test batch meet the specifications recommended by the Division of Bioequivalence.

Acceptable EER was dated 08/30/99.

18. CONCLUSIONS AND RECOMMENDATIONS:
Approvable

19. REVIEWER: Shing H. Liu, Ph.D.
DATE COMPLETED: December 23, 1999
Reviased January 28, 2000

Page(s) 13

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #3

1/28/2000

NOV 10

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-492 APPLICANT: Biovail Laboratories, Inc.

DRUG PRODUCT: Diclofenac Sodium Extended-release Tablets, 100 mg

A. The deficiencies presented below represent MINOR deficiencies.

1. The amendment dated April 28, 1999 submitted by the holder of the Drug Master File (DMF) for Diclofenac Sodium USP was reviewed in connection with your submission, and was found deficient again. The holder of the DMF, has been notified of the deficiencies.

   Please do not respond to this MINOR deficiency letter until you have been informed by rm. Co., Ltd. that their response to the deficiencies has been filed with the Agency.

2. Please amend your specifications for bulk drug substance release to include est. You do not have to conduct the test if your bulk drug substance supplier can provide you with a certification that no are used in the manufacturing process.

3. Please provide specifications and test results for residual solvents other than Please note that specifications include tests, analytical procedures and acceptance criteria.

4. Please tighten the range for individual tablets weight (p. 8767) to ± 5%.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

We have issued a methods validation request to the Northeast Regional Laboratory. Please prepare to submit samples to the Laboratory upon request.

Sincerely yours,

/S/

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

MAY - 4 1999

38. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 75-492 APPLICANT: Biovail Laboratories, Inc.

DRUG PRODUCT: Diclofenac Sodium Extended-release Tablets, 100 mg

A. The deficiencies presented below represent MAJOR deficiencies.

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-492

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-492 APPLICANT: BIOAVAIL LABS.

DRUG PRODUCT: DICLOFENAC SODIUM EXTENDED RELEASE TABLETS 100MG

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.5, at 37°C using USP Apparatus II(paddle) at 50 rpm. The test product should meet the following interim specifications:

Time(hours)	**% Dissolved**

The firm should also note the following comments for future submissions:

1. The elimination rate constant(Kel) should be calculated using a minimum of 3-time points.

2. The data in firm's diskette should read exactly the same as provided in hard copy. For instance, the AUC_{TAU} on the diskette was over 8 hours whereas the actual period was up to 24 hours.

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,

/S/

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

(1)

OFFICE OF GENERIC DRUGS

Division of Bioequivalence

ANDA#: 75-492 **SPONSOR:** Biovail Labs Inc.

DOSAGE FORM: **Diclofenac Sodium XR**
STRENGTH: 100 mg Tablet
TYPE OF STUDY: Fasting, Non-fasting and Steady-State Studies
STUDY SITE: Biovail Contract Research

STUDY SUMMARY: The 90% confidence intervals (in the Fasting and Steady-state studies) and the Test/Reference ratio (in the non-fasting study) are within acceptable limits. All three studies are complete.

DISSOLUTION: The dissolution testing was done by an acceptable non-USP method. Interim specifications have been recommended by the Division of Bioequivalence.

WAIVER: N/A

PRIMARY REVIEWER: Patrick E. Nwakama, Pharm.D. **BRANCH:** II

INITIAL: /S/ DATE: 2/17/99

BRANCH CHIEF: Shriniwas G. Nerurkar, Ph.D. **BRANCH:** II

INITIAL: /S/ DATE: 2/18/1999

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: /S/ DATE: 3/4/99

DIRECTOR, OFFICE OF GENERIC DRUGS

INITIAL: DATE:

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OVERNIGHT COURIER
BIOEQUIVALENCY TELEPHONE AMENDMENT

January 19, 1999

NEW CORRES

NC

Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application, 75-492
Diclofenac Sodium Extended-release Tablets, 100 mg

Dear Mr. Sporn,

On January 12, we fielded a telephone call from Nassar Muhmud and Dr.Patrick Nwakama concerning certain BE elements of our file. We are pleased to forward a solicited written confirmation of our conversation.

The substance of the Agency question revolved around the media used to perform dissolution testing for our product. Indeed, the Agency was interested to solicit Biovail's opinion why it used phosphate buffer for an acidic media as opposed to 0.1N HCl.

It should be noted that Biovail's product is not enterically coated and therefore does not fall within the BE guideline for diclofenac dissolution. Our product is an extended release matrix tablet, therefore we have selected a media that permits us to best demonstrate the dissolution profile of our product.

If you have any questions or comments, please contact me directly at telephone number (416) 285-6000 extension 213 or at fax number (905) 608-1616.

Yours respectfully,
BIOVAIL CORPORATION INTERNATIONAL

Martin Levy

Martin Levy, M.Sc., FBIRA
Manager, Corporate Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

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JAN 20 1999
GENERIC DRUGS

BIOVAIL CORPORATION INTERNATIONAL
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

Diclofenac Sodium XR Tablets
100 mg
ANDA #75-492
Reviewer: Patrick Nwakama
File name: 75492S.1098

Biovail Labs Inc.
34 Iturregui Avenue
Carolina, Puerto Rico
Submission Date:
October 30, 1998

REVIEW OF THREE *IN VIVO* BIOEQUIVALENCE STUDIES, AND *IN VITRO* DISSOLUTION TESTING DATA

The firm has submitted three *in vivo* bioequivalence studies (singl-dose fasting, single-dose non-fasting and steady-state multiple dose) and in vitro dissolution data comparing its test product, Diclofenac Sodium ER Tablets, 100 mg, to the reference listed drug, Ciba Geigy's Voltaren[R] XR Tablets, 100 mg. This is the **first generic** formulation of Voltaren[R] XR Tablets, 100 mg.

Introduction

Diclofenac is a non-steroidal anti-infammatory drug (NSAID) with analgesic and antipyretic activities. It is rapidly and completely absorbed after oral administration; peak concentrations in plasma are attained within 2 - 3 hours. Administration with food slows the rate but does not alter the extent of absorption. There is substantial first-pass effect, such that approximately 50% of diclofenac is available systemically. The drug is highly protein bound (99%), and its plasma half-life is 1 - 2 hours. Diclofenac is metabolized in the liver and the resulting metabolites are renally and biliary eliminated.

The reference listed drug is Voltaren[R] XR Tablets, 100 mg (Ciba-Geigy).

I. Single-dose Bioequivalence Study Under Fasting Conditions(Study # 2012):

A. Study Information:

Protocol #: 2012
IRB Approval: Yes
Consent Form Signed: Yes
Clinical Site:
Analytical Site:
Principal Investigator:

Study Dates:	Period I August 22, 1998 Period II September 5, 1998
Analysis Dates:	September 11 - 21, 1998
Study Design:	Randomized, two-way crossover design with washout period of 2 weeks.
Randomization Scheme:	AB: 1,7,9,11,12,13,14,16,17,23,28,30,31,34,35,36,38,39,40,41,42,47,48,50,56,57,59,60 BA: 2,3,5,6,8,10,15,18,19,20,21,22,24,2527,32,33,37,43,45,46,49,51,52,54,55
Treatments:	A: Diclofenac Sodium XR, 1x100 mg Tablets; Bioavail Corp.; Lot#:98CO23; Lot size Tablets; Manufacture Date: March 3, 1998; Assay: 100%; Content Uniformity: 98.7%. B: Voltaren[R] XR, 1x100 mg Tablets; Ciba Geigy; Lot# 165980; Expiry Date: April 2000; Assay: 98%; Content Uniformity: 97.7 %
Formulation of Test Drug:	Table 1
Subjects:	60 male subjects were enrolled per protocol.
Housing:	From the evening before dosing until after the 36 hour blood draw.
Dosing:	After 10-hour fast (7:00am), with 240 ml water. Blood samples (10 mL) collected at 0 h (pre-dose), 0.25, 0.5, 0.75,1.0,1.5,2.0,2.5, 3.0,4.0,5.0,6.0, 8.0,10.0,12.0, 14.0,16.0,18.0,20.0,24.0,and 36.0 h

B. **<u>Study Results</u>:**

1. **CLINICAL:**

Drop-outs: Subject #58 withdrew in Period I; subjects #26 and #44 withdrew prior to period II; subject #4 was dismissed prior to period II for overweight; and subjects #29 & #53 were dismissed in Period II for non-compliance.

2.

Thus, 54 subjects completed the study. Samples from all 54 subjects completing the study were analyzed.

Adverse Events: Subject #17 experienced mild abdominal pain in both periods; Subjects #16 & #58 had mild symptoms of pallor, sweat, and syncope in period I(test) which were considered non-drug related. Subject #44 had mild diarrhea in period I (test).

Protocol Deviations: Seventy-two(72) deviations were reported. Thirty-seven(37) occurred in period I (Subject #4 had outside limit weight; Subject #53 had outside the range BP; and the remaining 35 were due to sampling time delays). There were 35 deviations reported in period II (Subject #17 had no post-study lab work; Subjects #26, #43 & #50 did not complete their post-study medicals; and the remaining 31 were due to sampling time delays). Actual sampling times were used in all calculations.

2. **ANALYTICAL:**

Method:
Internal Standard:

Sensitivity(LOQ): 5.0 ng/mL

Specificity: No interfering peaks at retention times of Diclofenac or the internal standard.

Linearity: Standard Curve Range:
5.0 - 2560.35 ng/mL
Correlation Coefficient: $\geq$ 0.9989
QC Samples:
7.50,15.00,240.03,1920.26 ng/mL

Regression: (1/concentration) linear
Accuracy: Standard: 91.8 - 104.2%
QC Samples: 98.4 - 104.6%

Precision: Standard: 1.5 - 6.6%
QC Samples: 2.2 - 9.3%

Reassays: Twenty(20) samples from 6 subjects were reanalyzed - poor chromatogram (15), processing error(3) and sample switch suspected(2). Analytical repeats produced acceptable chromatograms and switch in samples was later confirmed.

The firm has provided the following pre-study method validation results:

Linearity: Standard Curve Range:
5.0 - 2560.0 ng/mL
QC Sample:
5.0,7.5,15.0,240.0,1920.0 ng/mL
Correlation Coefficient: $\geq$ 0.9992

Accuracy: **[Inter-day]**
Standard: 96.7 - 102.1%
QC Samples: 92.1 - 106.1%

[Intra-day]
QC Samples: 88.2 - 109.1%

Precision: **[Inter-day]**
Standard: 1.4 - 9.8%
QC Samples: 1.4 - 5.5%

[Intra-day]
QC Samples: 0.7 - 9.2%

Recovery: **Diclofenac**
7.50 ng/mL: 63.0%
15.0 ng/mL: 59.4%
240.0 ng/mL: 66.0%
1920.0 ng/mL: 68.3%

Internal Standard
49.4% (6.2% CV)

Stability:
a) In-process: stable for 4 h at room temperature (before extraction).
b) autosampler: stable for 48h

c) solution: in methanol, stable for 55 days at -25°C.

d) Freeze/Thaw: stable over 3 cycles

e) Long-term: stable in plasma at -25°C for 57 days.
Note: samples in the present study were stored for less than 57 days.

3. PHARMACOKINETICS / STATISTICS:

Diclofenac:

Mean Plasma Concentrations:	Table 2; Figures 1 & 2	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	$LAUC_{0-24h}$	101.0-109.3%
	$LAUC_{0-inf}$	92.4-106.3%
	LC_{max}	83.0-103.2%
Test/Reference Ratio:	AUC_{0-24h}	1.07 (0.76-1.49)
	AUC_{0-inf}	1.01 (0.63-1.39)
	C_{max}	1.02 (0.31-2.72)
AUC_{0-24h}/AUC_{0-inf} Ratio:	Test	0.97 (0.78-0.99)
	Reference	0.94 (0.75-0.99)
	(one subject's ratio =0.51)	

Comments:

1. The mean plasma diclofenac levels attained a maximum level of concentration at 5.0 hours(Table 2).

2. No subjects with zero-hour drug level. Five subjects(#17, #31, #33 & #48) had first scheduled post-dose time point as C_{max}. One subject(#12) had first measurable drug concentration as C_{max}. However, there were optimal sampling times before C_{max}. The reviewer also recalculated the pharmacokinetic parameters and 90% confidence intervals after dropping these 5 subjects and found them within the acceptable range.

3. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits. There were no statistically significant period, treatment or sequence effect for these parameters except the significant treatment effect for $LAUC_{0-t}$.

4. The elimination constant (Kel) and, therefore, AUC_{o-inf}, could not be calculated for the following:
   Subjects #23,35,45,46,48,& 60(test & reference)
   Subjects #6,15,16,23,25,33,34,35,& 37(test)
   Subjects#1,7,9,11,13,14,19,21,30,39,& 42(ref)
   The reviewer agrees with this observation. However, the reviewer does not agree with the estimation of Kel and $T_{1/2}$ for Subject #37(reference) using only two points and for Subject #22 (reference) despite poor correlation coefficient(r) value of -0.4. The confidence intervals for the AUC_{o-inf} is expected to be within the acceptance limits even when AUC_{o-inf} values for these two subjects are omitted because of the narrowness in the confidence intervals.

5. The mean half-life of the reference product is 2-fold higher than that of test.

6. The fasting study is acceptable.

II. Single-dose Bioequivalence Study Under Non-Fasting Conditions(Study # 1957-1):

A. Study Information:

Protocol #:	1957-1
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Analytical Site:	
Principal Investigator:	
Study Dates:	Period I June 14, 1998 Period II June 28, 1998 Period III July 12, 1998
Analysis Dates:	July 16 - 25, 1998
Study Design:	Randomized, three-way crossover design with washout period of 2 weeks.
Randomization Scheme:	ABC: 8,11,21 BCA: 2,5,18 ACB: 1,12,22 CBA: 3,7,10 CAB: 14,15,17 BAC: 4,9,13

Treatments: A: Diclofenac Sodium XR, 1x100 mg Tablets; Bioavail Corp.; Lot#:98CO23; **(test non-fasting)**

B: Voltaren[R] XR, 1x100 mg Tablets; Ciba Geigy; Lot# 165980; **(Reference non-fasting)**

C: Diclofenac Sodium XR, 1x100 mg Tablets;Lot#:98CO23; **(Test fasting)**

Formulation of Test Drug: Table 1

Subjects: 24 male subjects were enrolled per protocol.

Housing: From the evening before dosing until after the 36 hour blood draw.

Dosing: Treatments A & B:
Five minutes after completing a standard high-fat content breakfast with 240 ml water.

Treatment C:
After 10-hour fast (7:00am), with 240 ml water.

Sampling Times: Blood samples were taken at 0.0(pre-dose), 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, 24.0 & 36.0 hours.

B. Study Results:

1. CLINICAL:

Drop-outs: Subjects #6 and #16 withdrew prior to Period II due to personal reasons. Therefore, 22 subjects completed the study. Out of 1,427 samples obtained, 1,134 samples from first 18 subjects were analyzed per protocol.

Adverse Events: Subject #10 experienced mild transient dyspepsia during period I(test fasting)

Protocol Deviations: A total of 59 deviations were reported. Twenty-two(22) occurred in period I (one blood-draw miss and the remaining 21 were due to sampling time delays). There were 17 deviations reported in period II (one unfinished meal and and the remaining 16 were due to sampling time delays). There were twenty(20) deviations in period III, all due to sampling time delays. Actual sampling times were used in all calculations.

2.ANALYTICAL:

Method:
Internal Standard:
Sensitivity(LOQ): 5.0 ng/mL

Specificity: No interfering peaks at retention times of Diclofenac or the internal standard.

Linearity: Standard Curve Range:
5.0 - 2560.35 ng/mL
Correlation Coefficient: $\geq$ 0.9983
QC Samples:
7.50,15.00,240.07,1920.54 ng/mL

Regression: (1/concentration) linear

Accuracy:

Standard:	86.9 - 105.7%
QC Samples:	87.4 - 103.4%

Precision:

Standard:	1.7 - 6.7%
QC Samples:	2.3 - 12.8%

Reassays: One(1) sample from subject #5 was reanalyzed for poor chromatography.

2. PHARMACOKINETICS / STATISTICS:

Diclofenac:

Mean Plasma Concentrations: Table 3 ; Figures 3-8
Pharmacokinetic Parameters: Table 4

Test-fed/Ref. Fed Ratio: (means of ratios)		
	AUC_{o-t}	1.21 (0.77-3.27)
	AUC_{o-inf}	1.04 (0.77-1.50)
	C_{max}	1.05 (0.32-1.89)

AUC_{o-t}/AUC_{o-inf} Ratio:	Test Fasting	0.99 (0.98-0.99)
	Test Non-fasting	0.99 (0.96-0.99)
	Ref. Non-fasting	0.97 (0.81-0.99)

Commments:

1. The reviewer recalculated the kinetic parameters and ratios of means. The reported values are in good agreement with those obtained by the reviewer.

2. No subjects with zero-hour drug level, no subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug level as C_{max}.

3. Ratios of means for AUC_{o-t}, AUC_{o-inf}, and C_{max} between test (non-fasting) and reference (non-fasting) are within acceptable limits (Table #4).

4. The elimination constant (Kel) and, therefore, AUC_{inf}, could not be calculated for the following:
   Subject #2,10,21(test non-fasting)
   Subject #7,11,13,14,17,22(ref. non-fasting)
   Subject #9,10,13,21,22(test fasting)
   The reviewer agrees with this observation.

5. The non-fasting study is acceptable.

III. Two-Way, Steady-State, Multiple-Dose Bioequivalence Study Under Fasting Conditions(Study # 2011):

A. Study Information:

Protocol #:	2011
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Analytical Site:	
Principal Investigator:	

Study Dates:

Group I (subjects #1 - #37):
- Period I August 25, 1998
- Period II September 15, 1998

Group II(subjects #38 - #52):
- Period I August 29, 1998
- Period II September 19, 1998

Analysis Dates:	September 22 - October 2, 1998
Study Design:	Randomized, two-way crossover design with washout period of 2 weeks.
Randomization Scheme:	AB: 1,3,7,8,9,10,14,16,18,23,24,26,27,30,3334,36,37,38,45,47,48,49,52 BA: 2,5,6,12,13,15,19,21,22,25,28,31,32,39,40,41,42,43,46,50,51
Treatments:	A: Diclofenac Sodium XR, 1x100 mg Tablets; Bioavail Corp.; Lot#:98CO23. B: Voltaren[R] XR, 1x100 mg Tablets; Ciba Geigy; Lot# 165980.
Formulation of Test Drug:	Table 1
Subjects:	52 male subjects were enrolled per protocol criteria.
Housing:	From the evening before dosing until after the 36 hour blood draw.
Dosing:	Single dose on day #1 - day #7 after 10-hour fast (7:00am), with 240 ml water.
Sampling Times:	Blood samples (10 mL) were collected on Day 1: 0 h (pre-dose); Day 4: 0 h(pre-dose); Day 5: 0 h(pre-dose), Day 6: 0 h(pre-dose), and on Day 7 at 0.0 h, 0.25,0.50,0.75,1.0,1.5,2.0,2.5,3.0,4.0,5.0,6.0,8.0,10.0,12.0,14.0,16.0; Day 8: 18.0,20.0,and 24.0 hours.

B. **Study Results:**

1. **CLINICAL:**

Drop-outs: Subjects #4 and #29 did not return for period II; subjects #35 and #44 withdrew from period I for personal reasons; subject #20 withdrew from period II for personal reasons; subjects #11 and #17 dismissed from period II for vomiting (test-fasting) and non-compliance, respectively. Therefore, 45 subjects completed the study. Plasma samples from these 45 subjects were analyzed.

Adverse Events: Forty-three(43) events occurred in 21 subjects. These include abdominal pain, headache, N/V, epistaxis, pruritis, rhinitis, dizziness, diarrhea etc. All events were mild with exception of two(2) moderate cases of pruritis and vomiting. The events were comparable in both test and reference. Subject #11 experienced 2 episodes of nausea and 1 episode of vomiting and was dismissed Day 3(period II).

Protocol Deviations: A total of 104 deviations were reported. Seventy-eight (78) were from blood sampling; 14 deviations were meal-related, 9 involved blood-work misses, 2 were post-study medical misses and 1 was incomplete health status monitoring.

2.ANALYTICAL:

Method: HPLC/UV
Internal Standard: Indomethacin

Sensitivity(LOQ): 5.0 ng/mL

Specificity: No interfering peaks at retention times of Diclofenac or the internal standard.

Linearity:	Standard Curve Range: 5.00 - 2560.35 ng/mL	
	Correlation Coefficient:	$\geq$ 0.9961
	QC Samples: 7.50,15.00,240.03,1920.26 ng/mL	
Regression:	(1/concentration) linear	
Accuracy:	Standard:	91.6 - 104.0%
	QC Samples:	99.5 - 106.0%
Precision:	Standard:	2.7 - 7.0%
	QC Samples:	4.7 - 7.2%
Reassays:	A total of 13 samples from 5 subjects were reassayed- 6(poor chromatography), 5(processing error) and 2(internal standard-related).	

3. PHARMACOKINETICS / STATISTICS:

Diclofenac:

Mean Plasma Concentrations:	Table 5; Figures 9 & 10	
Pharmacokinetic Parameters:	Table 5	
90% Confidence Intervals:	$LAUC_{0-24h}$	101.1-111.1%
	LC_{max}	84.5-107.1%
Test/Reference Ratio:	AUC_{0-24h}	1.08 (0.77-1.66)
	C_{max}	1.07 (0.36-2.42)
	C_{min}	0.30 (0.00-1.09)
	C_{ave}	1.08 (0.77-1.66)
	Degree of Fluctuation	0.90 (0.78-1.42)

Commments:

1. The mean plasma diclofenac levels for the test product and reference products attained maximum level of concentrations on Day 7 (5.00 h)(Table 5).

2. The reviewer's recalculated pharmacokinetic values were in agreement with those obtained by the firm. The 90% confidence intervals calculated after omitting subject #42 with first measurable drug level as C_{max} are within the acceptable limits.

3. The firm has confirmed the attainment of steady-state level by performing analysis of variance (ANOVA) on log-transformed pre-dose levels (Days 4,5,6 and 7).

4. The reviewer analyzed submitted data for group effects using model GRP SEQ SEQ*GRP SUB(SEQ*GRP) PER(GRP) TRT TRT*GRP. There was no significant treatment*group interaction noted with AUC_{0-24h} and C_{max}. Hence, trt*group was dropped from the model and the data reanalyzed.

5. There was a significant difference in arithmetic means of the C_{min} values between the two formulations resulting in a low ratio(Table 5).

6. The multiple-dose biostudy is acceptable.

***In Vitro* Dissolution Testing:**

The dissolution testing was done using a dissolution method developed by the firm. Four phosphate buffer solutions (pH 1.5, 4.5, 6.5, & 7.5) and water were separately used as dissolution media (Tables 5a-e). The dissolution data were provided for the same batches used in the *in vivo* biostudies. The firm has proposed method using water as the medium with the following specifications (Table 5a):

Time(h)	Specification

Comments:

1. There is at present no approved USP Dissolution method or specifications for Diclofenac sodium XR tablets.

2. Sampling times were done hourly during the entire 16-hour sampling period.

3. Phosphate buffers used range from pH 1.5 - 7.5 while typical buffered aqueous solutions have pH 4 -8.

4. The test product is not scored so no dissolution testing was done for halved tablets.

5. After reviewing the dissolution data, the firm's proposed method (water medium) appears to yield the best dissolution profile but the intestinal fluid milieu is mostly simulated by buffer (pH 7.5).

6. The dissolution testing is acceptable with some modifications in future dissolution testing. The following method will be proposed to the firm:

   The dissolution testing should be conducted in 900 mL of pH 7.5 phosphate buffer at 37°C using USP Apparatus II(paddle) at 50 rpm. The test product should meet the following interim specifications:

Time(hours)	**% Dissolved**
8	%
	%

Recommendations:

I. The in vivo bioequivalence study conducted under fasting conditions by Bioavail Labs on its Diclofenac sodium XR tablets, 100mg, lot # 98CO23, comparing it to the reference product, Voltaren[R] XR tablets, 100mg, lot # 165980, manufactured by Ciba Geigy, has been found acceptable by the Division of Bioequivalence.

II. The in vivo bioequivalence study conducted under non-fasting conditions by Bioavail Labs on its Diclofenac sodium XR tablets, 100mg, lot # 98CO23, comparing it to the reference product, Voltaren[R] XR tablets, 100mg, lot # 165980, manufactured by Ciba Geigy, has been found acceptable by the Division of Bioequivalence.

III. The in vivo bioequivalence study conducted under steady state conditions by Bioavail Labs on its Diclofenac sodium XR tablets, 100mg, lot # 98CO23, comparing it to the reference product, Voltaren[R] XR tablets, 100mg, lot # 165980, manufactured by Ciba Geigy, has been found acceptable by the Division of Bioequivalence.

IV. The in vitro dissolution testing submitted by the firm on its Diclofenac sodium XR tablets, 100mg, lot #98CO23, is acceptable. The dissolution testing should be conducted in 900 mL pH 7.5 phosphate buffer at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following interim specifications:

Time (hours)	% Dissolved

/S/

Patrick Nwakama, Pharm.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
for FT INITIALED S. NERURKAR

/S/ Date 2/18/99

Concur: /S/ Date 3/4/99

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

Table 1

Quantitative Composition of Diclofenac Sodium XR 100mg Tablets

Ingredient	**100 mg XR Tablet (mg/tablet)**
Diclofenac Sodium,	100.00
Lactose Anhydrous,	157.95
Hydroxyethyl Cellulose,	47.99
Opadry II(Pink)	6.41
Opadry Clear)	2.20
Magnesium Stearate,	3.98
Providone,	1.41
Colloidal Silicon Dioxide,	0.80
Talc,	7.99
Total Tablet Weight	**328.73**

TABLE 2

MEAN PLASMA DICLOFENAC LEVELS (ng/mL) FOR TEST(1) AND REFERENCE(2) PRODUCTS (100 MG TABLETS) IN FASTING STUDY (N=54)

TIME(HR)	MEAN1	SD1	MEAN2	SD2	RMEAN12
0.00	00.00	00.00	00.00	00.00	00.00
0.25	85.39	125.21	158.21	245.71	0.54
0.50	127.69	151.83	222.68	245.23	0.57
0.75	163.93	156.29	216.31	204.25	0.76
1.00	186.88	148.40	194.17	147.96	0.96
1.50	238.27	131.67	180.65	118.70	1.32
2.00	273.01	106.61	180.74	109.50	1.51
2.50	299.33	128.26	181.22	91.48	1.65
3.00	277.93	107.85	187.59	89.68	1.48
4.00	240.90	99.46	180.39	118.55	1.34
5.00	311.11	155.38	303.38	255.37	1.03
6.00	238.31	126.27	207.19	142.29	1.15
8.00	178.58	87.00	117.26	86.02	1.52
10.00	167.41	106.09	172.93	142.14	0.97
12.00	75.42	45.25	112.33	80.24	0.67
14.00	45.97	34.31	71.25	42.96	0.65
16.00	25.16	19.17	39.47	26.36	0.64
18.00	12.87	11.48	22.22	17.77	0.58
20.00	8.61	9.20	15.79	13.36	0.55
24.0	8.44	11.90	16.99	17.37	0.50
36.00	0.39	2.21	2.18	5.61	0.18

UNIT: PLASMA LEVEL=NG/ML TIME= HOURS

ARITHMETIC MEANS AND RATIOS

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEANS12
AUCT	2747.97	571.61	2642.12	665.67	1.04
AUCI	2905.19	617.68	2929.05	688.47	0.99
CMAX	423.56	113.33	490.13	225.74	0.86
TMAX	4.04	2.71	4.31	3.47	0.94
THALF	5.19	6.35	11.87	22.15	0.44
KEL	0.29	0.19	0.18	0.18	1.61
LAUCT	7.89	0.19	7.85	0.25	1.01
LAUCI	7.95	0.21	7.96	0.23	1.00
LCMAX	6.02	0.26	6.09	0.47	0.99
TLAG	0.13	0.23	0.30	0.54	0.43
TMAXADJ	3.89	2.74	3.73	3.21	1.04

LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSMEAN2	LSMEAN1	LSMEAN12	CIUPP	CILOW
AUCT	2640.30	2747.86	1.04		
CMAX	489.99	423.75	0.86		
LAUCT	7.85	7.90	1.01	109	101
LCMAX	6.09	6.02	0.99	103	83
AUCI	2896.48	2848.01	0.98		
LAUCI	7.94	7.94	1.00	106	92

TABLE 3

MEAN PLASMA DICLOFENAC LEVELS (ng/mL) FOR TEST AND REFERENCE PRODUCTS (100 MG TABLETS) IN NON-FASTING STUDY (N=22)

TIME(HR)	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
0.00	00.00	00.00	00.00	00.00	00.00	0.00	0.00
0.25	61.15	68.59	00.00	00.00	0.98	2.88	...
0.50	143.04	147.60	2.56	5.66	19.52	74.54	55.88
0.75	166.59	123.16	13.00	18.18	95.77	220.49	12.81
1.00	191.10	113.22	22.33	19.94	108.89	234.73	8.56
1.50	229.40	125.56	102.65	168.67	128.76	372.65	2.23
2.00	266.45	122.58	184.68	210.47	96.06	198.74	1.44
2.50	257.14	110.89	197.00	158.52	110.97	173.68	1.30
3.00	240.69	94.59	271.73	179.60	152.37	188.12	0.89
4.00	208.23	89.81	262.49	163.59	150.92	145.89	0.79
5.00	307.38	140.37	383.47	256.40	164.59	128.61	0.80
6.00	249.03	129.45	275.25	193.62	147.90	145.23	0.90
8.00	235.43	132.49	161.72	104.88	178.34	388.31	1.46
10.00	147.32	70.28	148.27	121.78	225.28	226.63	0.99
12.00	70.96	46.47	69.38	51.39	100.57	85.59	1.01
14.00	41.75	31.89	42.84	52.18	60.15	52.49	0.97
16.00	23.61	17.92	23.71	23.62	36.13	26.96	1.00
18.00	12.92	11.74	14.73	18.15	20.98	16.35	0.88
20.00	8.08	7.75	8.29	13.24	15.28	14.01	1.04
24.00	5.55	6.07	4.30	5.72	22.10	46.27	1.29
36.00	0.00	0.00	0.00	0.00	1.75	4.55	0.00

TIME(HR)	RMEAN13	RMEAN23
0.00	00.00	00.00
0.25	62.40	00.00
0.50	7.30	00.00
0.75	1.74	0.14
1.00	1.75	0.21
1.50	1.78	0.80
2.00	2.77	1.92
2.50	2.32	1.78
3.00	1.57	1.78
4.00	1.38	1.74
5.00	1.87	2.33
6.00	1.68	1.86
8.00	1.32	0.91
10.00	0.65	0.66
12.00	0.71	0.69
14.00	0.69	0.71
16.00	0.65	0.66
18.00	0.62	0.70
20.00	0.53	0.54
24.00	0.25	0.19
36.00	0.00	0.00

UNIT: PLASMA LEVEL = NG/ML TIME = HOURS
1 = TEST FASTING
2 = TEST NON-FASTING
3 = REFERENCE NON-FASTING

TABLE 4

DICLOFENAC ARITHMETIC AND LS MEANS AND RATIOS IN NON-FASTING STUDY (N=22)

ARITHMETIC MEANS AND RATIOS

PARAMETER	MEAN2	SD2	MEAN3	SD3	MEAN1	SD1	RMEAN12
AUCT	2467.69	712.19	2276.21	1022.40	2703.94	664.89	1.09
AUCI	2539.33	749.19	2620.10	1100.54	2886.81	697.10	1.14
CMAX	521.70	271.56	568.28	425.24	430.79	91.51	0.83
TMAX	5.28	2.80	6.38	5.57	3.63	2.28	0.69
TLAG	0.61	0.31	0.79	0.54	0.15	0.37	0.25
TMAX(ADJ)	4.67	2.73	5.58	5.43	3.47	2.16	0.74
THALF	2.78	0.94	4.20	3.62	3.32	1.62	1.19
KEL	0.28	0.11	0.25	0.13	0.26	0.12	0.93
LAUCT	7.77	0.28	7.64	0.45	7.87	0.24	1.01
LAUCI	7.80	0.28	7.80	0.39	7.94	0.24	1.02
LCMAX	6.14	0.48	6.16	0.58	6.04	0.22	0.98

UNIT: AUC = NG HR/ML; CMAX = NG/ML; TMAX = HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE ARITHMETIC MEANS AND RATIOS

PARAMETER	RMEAN13	RMEAN23
AUCT	1.19	1.08
AUCI	0.46	0.97
CMAX	0.76	0.92
TMAX	0.57	0.83
TLAG	0.19	0.77
TMAX(ADJ)	0.62	0.84
THALF	0.79	0.66
KEL	1.04	1.12
LAUCT	1.03	1.02
LAUCI	1.02	1.00
LCMAX	0.98	0.99

UNIT: AUC = NG HR/ML; CMAX = NG/ML; TMAX = HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND RATIOS

PARAMETER	LSMEAN2	LSMEAN3	LSMEAN1	RLSMEAN12	RLSMEAN13	RLSMEAN23
AUCT	2467.69	2276.21	2703.94	1.09	1.19	1.08
CMAX	521.70	568.28	430.79	0.83	0.76	0.92
LAUCT	7.77	7.64	7.87	1.01	1.03	1.02
LCMAX	6.14	6.16	6.04	0.98	0.98	0.99
AUCI	2480.95	2501.83	2706.87	1.09	1.08	0.99
LAUCI	7.78	7.77	7.88	1.01	1.01	1.00

1 = TEST FASTING
2 = TEST NON-FASTING
3 = REFERENCE NON-FASTING

TABLE 5

MEAN PLASMA DICLOFENAC LEVELS (ng/mL) FOR TEST AND REFERENCE PRODUCTS (100 MG TABLETS) IN MULTIPLE DOSE STUDY (N=45)

TIME(HR)	MEAN1	SD1	MEAN2	SD2	RMEAN12
Day 1 (0.00 h)	0.00	0.00	0.00	0.00	0.00
Day 4 (0.00 h)	7.38	7.58	19.90	17.54	0.37
Day 5 (0.00 h)	7.63	8.47	16.48	14.54	0.46
Day 6 (0.00 h)	5.68	6.70	15.34	11.51	0.37
Day 7 (0.00 h)	8.15	9.99	16.37	13.39	0.50
(0.25 h)	144.17	177.65	164.13	193.04	0.88
(0.50 h)	163.79	149.69	241.75	185.04	0.68
(0.75 h)	174.00	145.59	204.17	151.42	0.85
(1.00 h)	195.81	155.37	176.56	113.64	1.11
(1.50 h)	231.37	128.14	178.23	117.05	1.29
(2.00 h)	253.87	96.70	166.62	91.19	1.52
(2.50 h)	286.77	103.92	164.18	67.56	1.75
(3.00 h)	279.21	114.38	159.67	59.75	1.75
(4.00 h)	291.00	146.21	157.29	82.53	1.85
(5.00 h)	317.45	158.10	356.01	304.94	0.89
(6.00 h)	245.38	163.68	229.54	174.00	1.07
(8.00 h)	160.93	85.38	111.05	72.00	1.45
(10.0 h)	127.81	110.61	127.61	105.59	1.00
(12.0 h)	49.16	25.77	93.51	68.17	0.53
(14.0 h)	27.42	14.25	60.74	36.50	0.45
(16.0 h)	16.90	9.51	35.87	22.73	0.47
(18.0 h)	10.51	8.06	25.37	17.64	0.41
(20.0 h)	6.46	6.80	17.23	12.88	0.37
(24.0 h)	5.44	6.15	17.29	14.70	0.31

UNIT: PLASMA LEVEL=NG/ML TIME= HOURS

ARITHMETIC MEANS AND RATIOS

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUC_{0-24H}	2579.25	47.63	2456.17	47.63	1.08
CAVG	107.59	20.40	101.96	23.43	1.08
CMAX	481.31	24.75	526.38	24.75	0.93
CMIN	5.67	1.53	17.44	1.53	0.30
TMAX	3.80	0.39	4.53	0.39	0.83
DEG.FLUC	449.36	117.40	498.28	191.48	0.90

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSMEAN2	LSMEAN1	CIUPP	CILOW
$LAUC_{0-24H}$	7.78	7.84	111	101
LCMAX	6.18	6.13	107	85

Table 5a. In Vitro Dissolution Testing

Drug (Generic Name): Diclofenac XR Tablets
Dose Strength: 100 mg
ANDA No.: 75-492
Firm: Biovail Laboratories Inc.
Submission Date: October 30, 1998
File Name: 75-492S.1098

I. Conditions for Dissolution Testing: NON-USP METHOD

USP XXIII Basket: x Paddle: RPM: 50 rpm
No. Units Tested: 12 (2 runs of 6 tablets each)
Medium: Phosphate Buffer [pH 1.5,4.5,6.5,7.5] or Water Volume: 900 mL
Specifications:
Reference Drug: Voltaren[R] (Ciba-Geigy)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 98C023 Strength(mg) 100 mg WATER			Reference Product Lot # 165980 Strength(mg) 100 mg WATER		
	Mean %	Range	%CV	Mean %	Range	%CV
1	18		3.3	27		2.2
2	29		4.1	38		2.4
3	39		4.6	47		2.1
4	48		4.6	54		1.9
5	56		4.8	60		2.0
6	64		5.0	66		2.1
7	72		4.3	71		2.0
8	79		3.9	75		1.9
9	85		3.6	78		2.2
10	91		4.3	81		2.1
11	98		3.8	84		1.9
12	100		2.3	86		2.0
13	102		1.5	88		2.0
14	102		1.4	90		1.8
15	103		1.3	91		1.8
16	103		1.3	93		1.8

Table 5b. In Vitro Dissolution Testing

Drug (Generic Name): Diclofenac XR Tablets
Dose Strength: 100 mg
ANDA No.: 75-492
Firm: Biovail Laboratories Inc.
Submission Date: October 30, 1998
File Name: 75-492S.1098

I. Conditions for Dissolution Testing: NON-USP METHOD

USP XXIII Basket: x Paddle: RPM: 50 rpm
No. Units Tested: 12 (2 runs of 6 tablets each)
Medium: Phosphate Buffer [pH 1.5,4.5,6.5,7.5] or Water Volume: 900 mL
Specifications:
Reference Drug: Voltaren[K] (Ciba-Geigy)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 98C023 Strength(mg) 100 mg (pH 1.5) BUFFER			Reference Product Lot # 165980 Strength(mg) 100 mg (pH 1.5) BUFFER		
	Mean %	Range	%CV	Mean %	Range	%CV
1	0.2		50.0	0.5		20.0
2	0.3		33.3	0.6		33.3
3	0.5		20.0	0.7		42.9
4	0.7		14.3	0.8		37.5
5	0.8		25.0	0.8		37.5
6	0.9		22.2	0.9		44.4
7	1.0		10.0	0.9		44.4
8	1.2		8.3	1.0		40.0
9	1.3		7.7	1.0		40.0
10	1.4		7.1	1.1		36.4
11	1.5		6.7	1.1		36.4
12	1.5		6.7	1.1		36.4
13	1.6		6.3	1.2		33.3
14	1.7		5.9	1.2		33.3
15	1.7		5.9	1.2		33.3
16	1.8		5.6	1.3		38.5

Table 5c In Vitro Dissolution Testing

Drug (Generic Name): Diclofenac XR Tablets
Dose Strength: 100 mg
ANDA No.: 75-492
Firm: Biovail Laboratories Inc.
Submission Date: October 30, 1998
File Name: 75-492S.1098

I. Conditions for Dissolution Testing: NON-USP METHOD

USP XXIII Basket: x Paddle: RPM: 50 rpm
No. Units Tested: 12 (2 runs of 6 tablets each)
Medium: Phosphate Buffer [pH 1.5,4.5,6.5,7.5] or Water Volume: 900 mL
Specifications:
Reference Drug: Voltaren[R] (Ciba-Geigy)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 98C023 Strength(mg) 100 mg (pH 4.5) BUFFER			Reference Product Lot # 165980 Strength(mg) 100 mg (pH 4.5) BUFFER		
	Mean %	Range	%CV	Mean %	Range	%CV
1	3.0		3.3	4.0	3.6-4.8	7.5
2	4.7		4.3	6.0		6.7
3	6.0		3.3	6.7		6.0
4	6.8		4.4	7.0		7.1
5	7.7		3.9	7.1		7.0
6	8.5		3.5	7.3		6.8
7	9.2		3.3	7.3		6.8
8	9.9		3.0	7.4		6.8
9	10.6		2.8	7.5		6.7
10	11.3		2.7	7.5		6.7
11	12.0		2.5	7.6		6.6
12	12.7	1	2.4	7.6		6.6
13	13.4	1	3.0	7.7		6.5
14	14.1	1	2.8	7.6		6.6
15	14.7	1	2.7	7.7		6.5
16	15.5	1	3.2	7.7		6.5

Table 5d In Vitro Dissolution Testing

Drug (Generic Name): Diclofenac XR Tablets
Dose Strength: 100 mg
ANDA No.: 75-492
Firm: Biovail Laboratories Inc.
Submission Date: October 30, 1998
File Name: 75-492S.1098

I. Conditions for Dissolution Testing: NON-USP METHOD

USP XXIII Basket: x Paddle: RPM: 50 rpm
No. Units Tested: 12 (2 runs of 6 tablets each)
Medium: Phosphate Buffer [pH 1.5,4.5,6.5,7.5] or Water Volume: 900 mL
Specifications:
Reference Drug: Voltaren[R] (Ciba-Geigy)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 98C023 Strength(mg) 100 mg (pH 6.5) BUFFER			Reference Product Lot # 165980 Strength(mg) 100 mg (pH 6.5) BUFFER		
	Mean %	Range	%CV	Mean %	Range	%CV
1	14		3.6	19	18-20	2.6
2	22		3.6	27		1.9
3	29		4.1	33		1.8
4	36		3.9	38		1.8
5	42		3.8	42		1.7
6	48		4.4	46		2.0
7	53		4.2	48		2.1
8	59		4.2	51		2.0
9	64		4.4	53		2.3
10	68		3.8	55		2.5
11	72		4.0	56		2.3
12	76		3.9	58		2.6
13	80		3.9	59		2.9
14	83		3.6	60		2.8
15	85		3.3	61		2.8
16	87		2.9	62		2.7

Table 5e In Vitro Dissolution Testing

Drug (Generic Name): Diclofenac XR Tablets
Dose Strength: 100 mg
ANDA No.: 75-492
Firm: Biovail Laboratories Inc.
Submission Date: October 30, 1998
File Name: 75-492S.1098

I. Conditions for Dissolution Testing: NON-USP METHOD

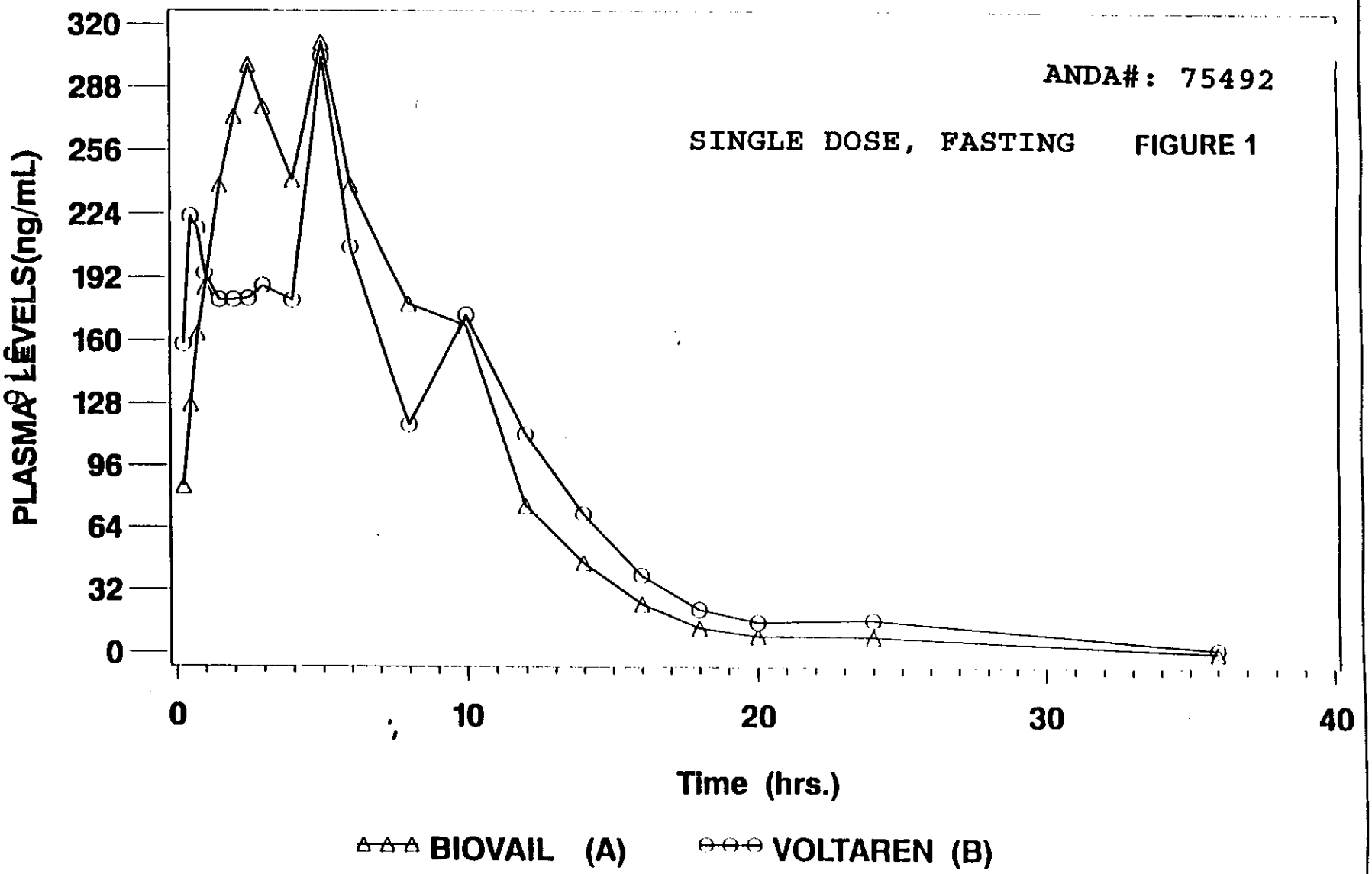
USP XXIII Basket: x Paddle: RPM: 50 rpm
No. Units Tested: 12 (2 runs of 6 tablets each)
Media: Phosphate Buffer [pH 1.5,4.5,6.5,7.5] or Water Volume: 900 mL
Specifications:
Reference Drug: Voltaren[R] (Ciba-Geigy)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 98C023 Strength(mg) 100 mg (pH 7.5) BUFFER			Reference Product Lot # 165980 Strength(mg) 100 mg (pH 7.5) BUFFER		
	Mean %	Range	%CV	Mean %	Range	%CV
1	14		2.9	19		3.7
2	23		3.5	28		3.2
3	31		3.2	34		3.2
4	38		3.7	40		2.5
5	44		3.9	45		2.7
6	51		4.1	50		2.4
7	57		4.0	54		2.4
8	62		4.4	57		2.5
9	68		4.3	61		2.3
10	73		4.5	64		2.2
11	77		4.4	66		2.1
12	81		4.7	69		2.3
13	85		4.5	71		2.1
14	89		4.3	73		2.1
15	93		4.2	75		2.0
16	96		4.2	77		2.2

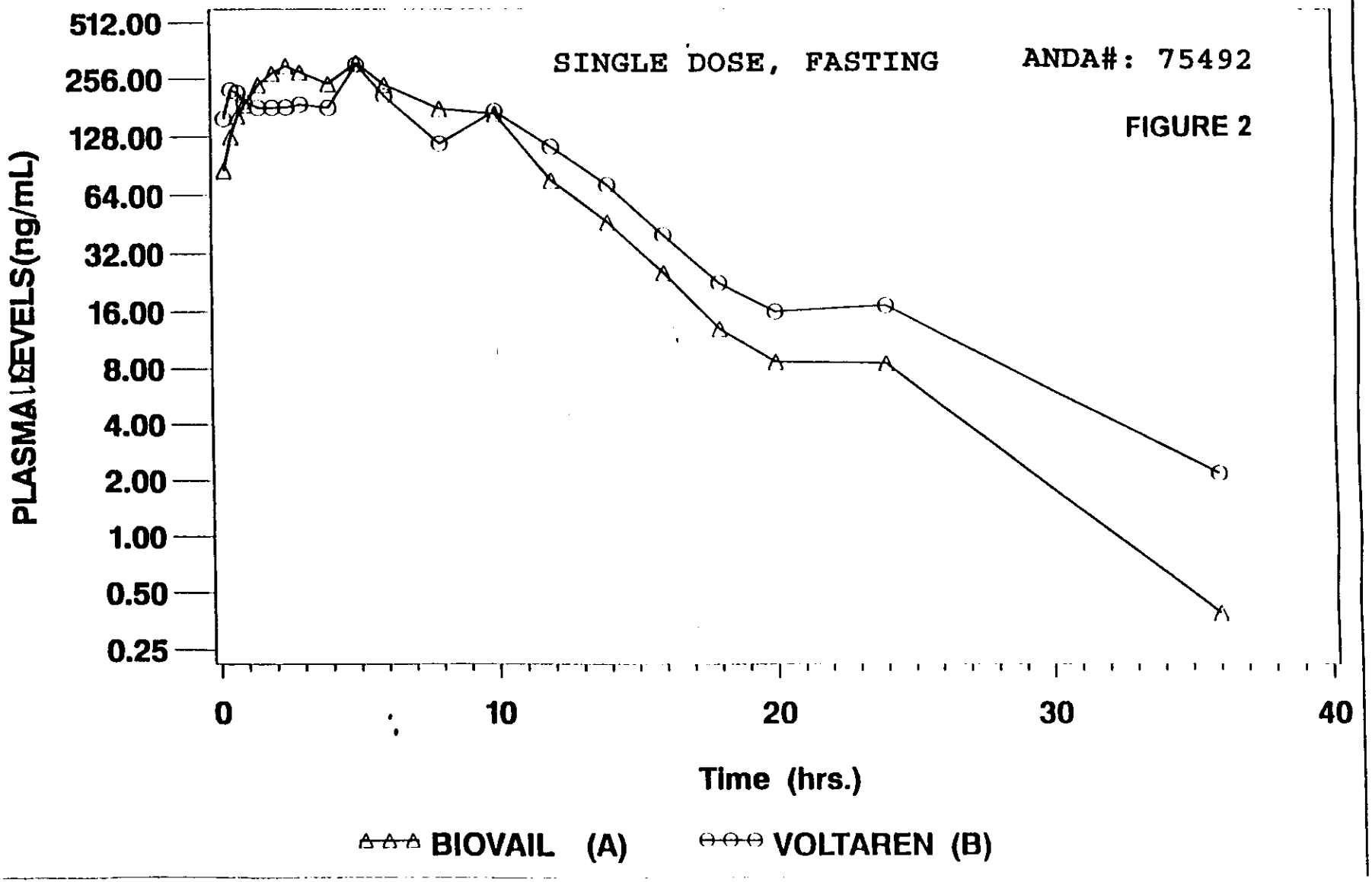
MEAN PLASMA DICLOFENAC CONCENTRATIONS

STUDY # (2012)



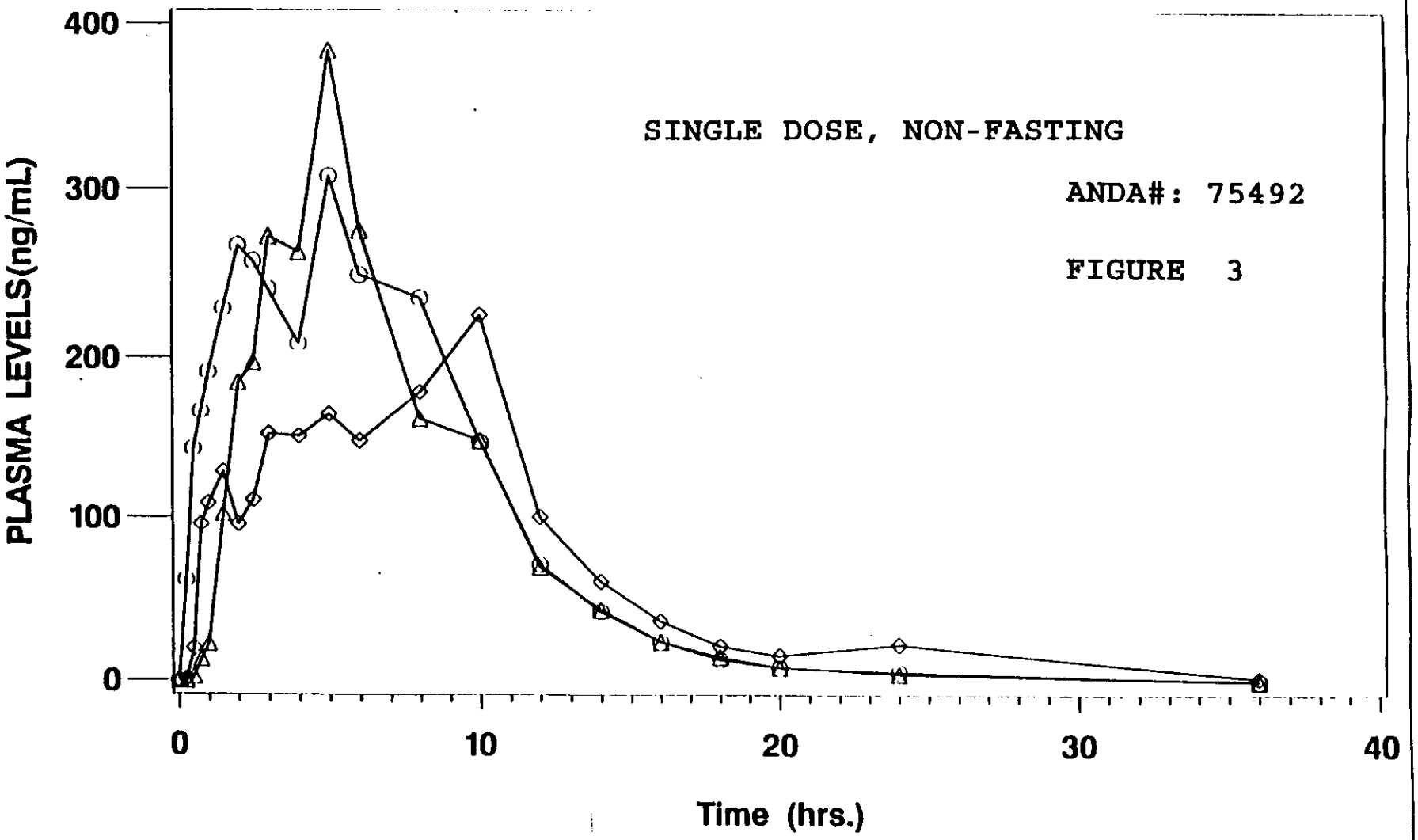
SEMI LOG MEAN PLASMA DICLOFENAC CONCENTRATIONS

STUDY # (2012)



MEAN PLASMA DICLOFENAC CONCENTRATIONS

(STUDY # 1957 – 1)



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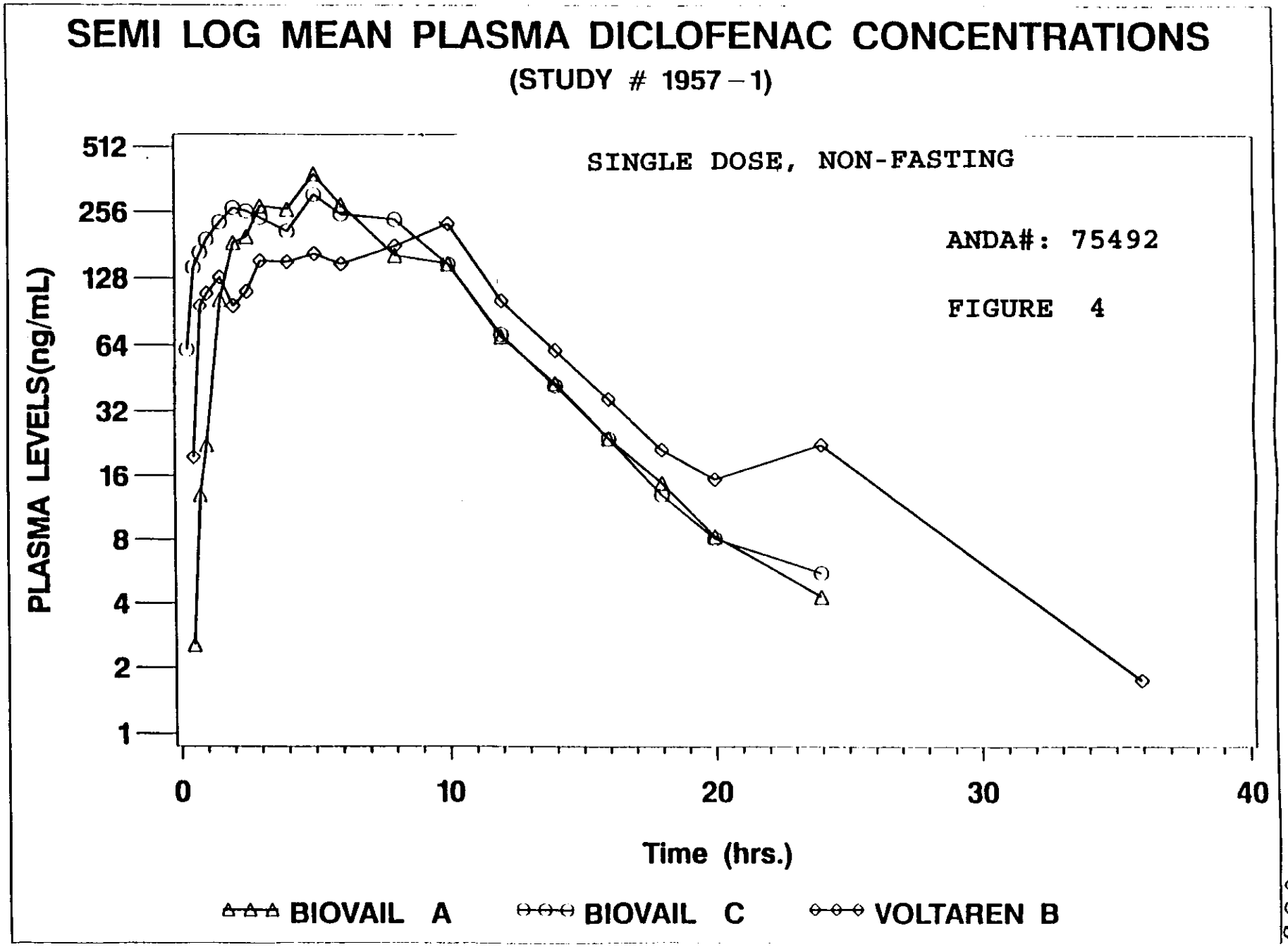
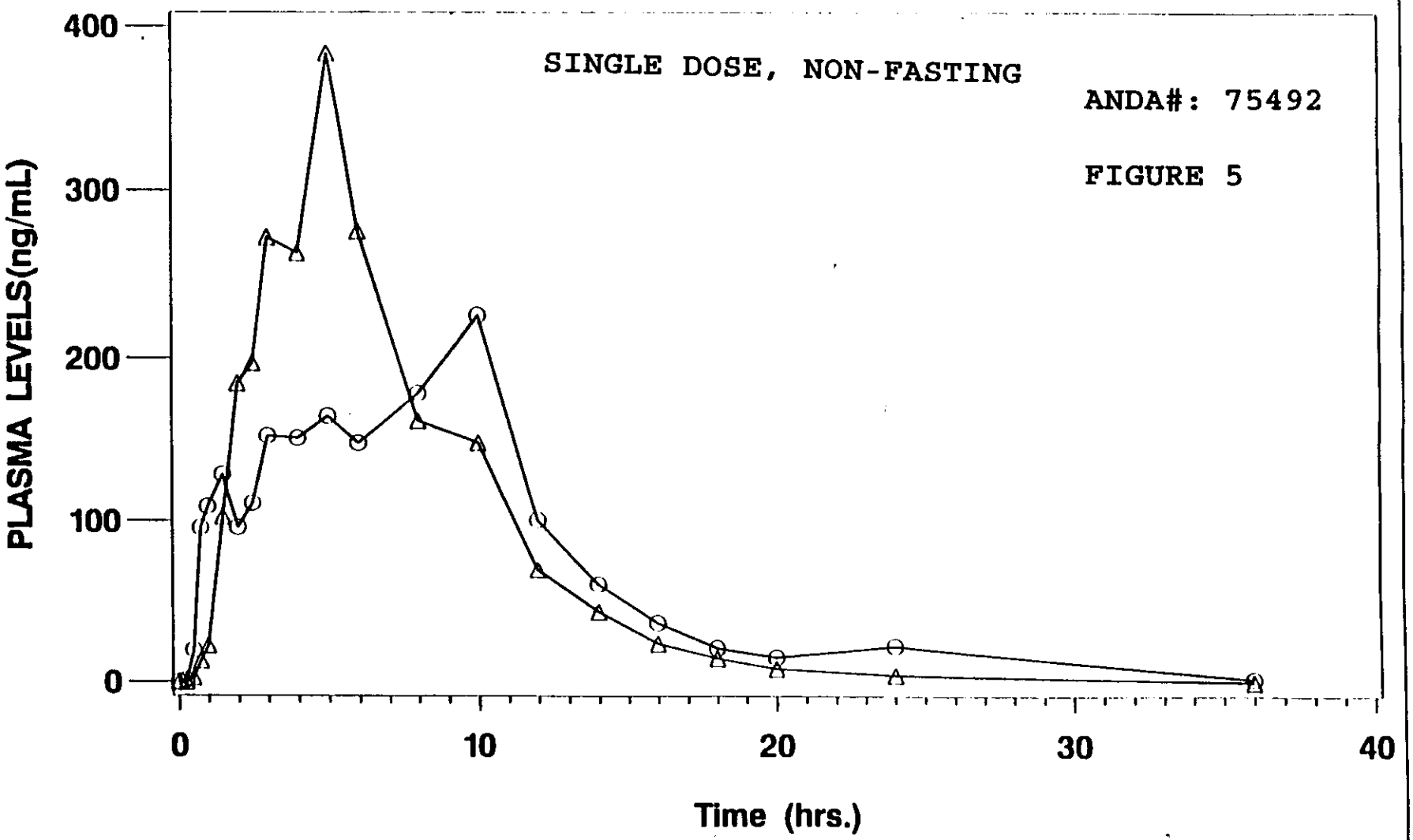

SEMI LOG MEAN PLASMA DICLOFENAC CONCENTRATIONS
(STUDY # 1957 – 1)
SINGLE DOSE, NON-FASTING
ANDA#: 75492
FIGURE 4
PLASMA LEVELS(ng/mL)
512
256
128
64
32
16
8
4
2
1
0
10
20
30
40
Time (hrs.)
BIOVAIL A
BIOVAIL C
VOLTAREN B

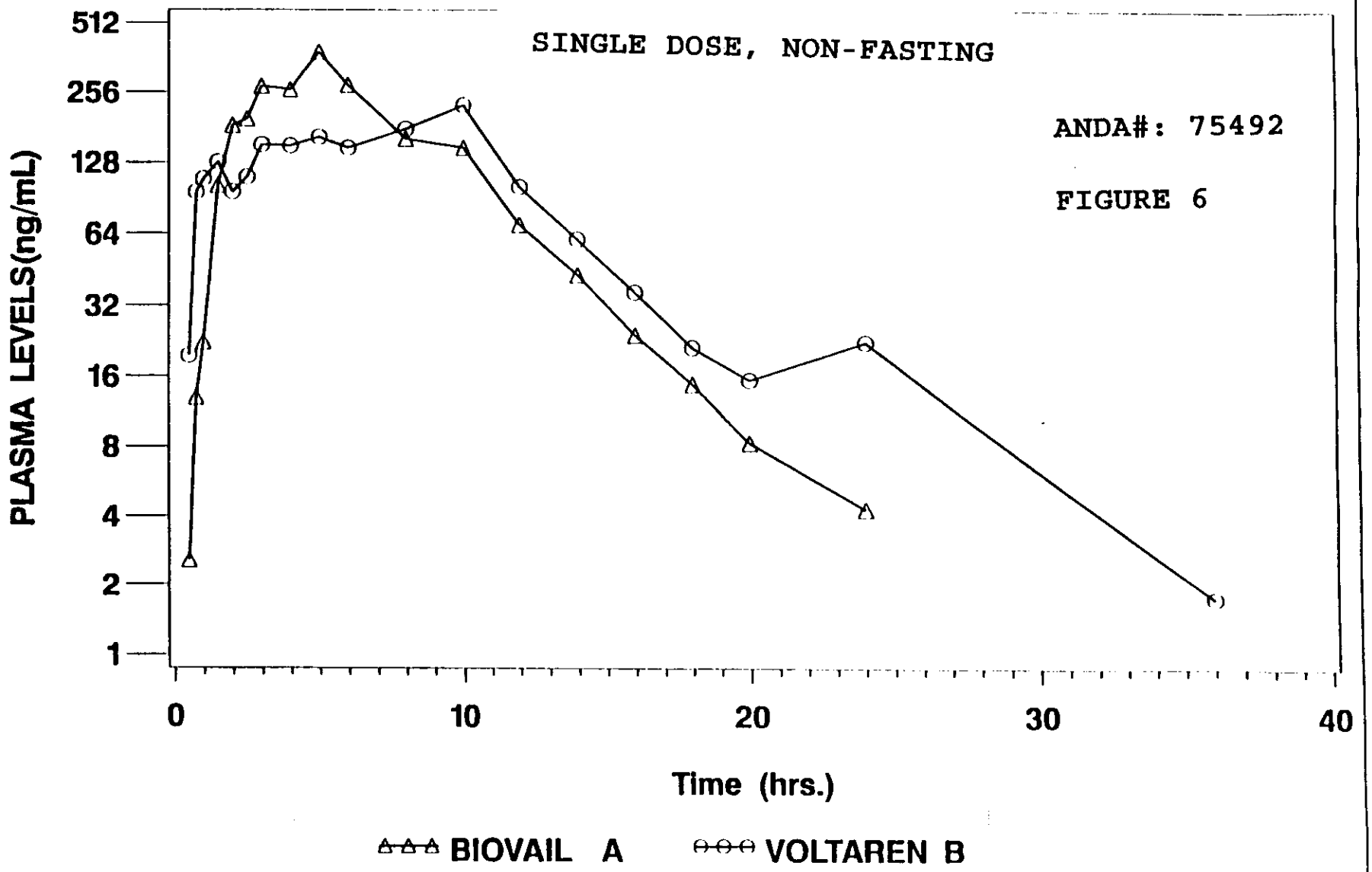
MEAN PLASMA DICLOFENAC CONCENTRATIONS

(STUDY # 1957 – 1)



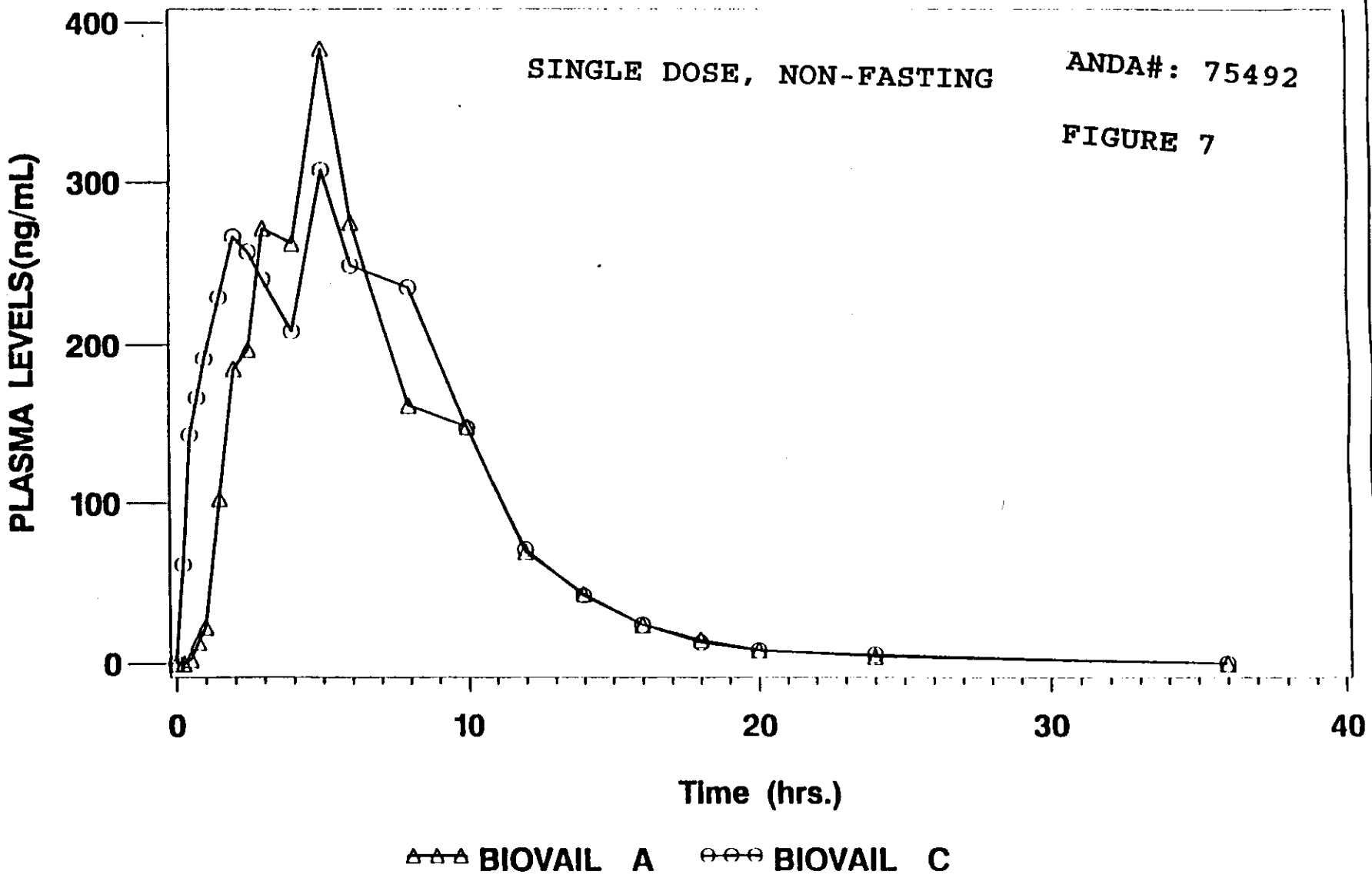
SEMI LOG MEAN PLASMA DICLOFENAC CONCENTRATIONS

(STUDY # 1957 – 1)



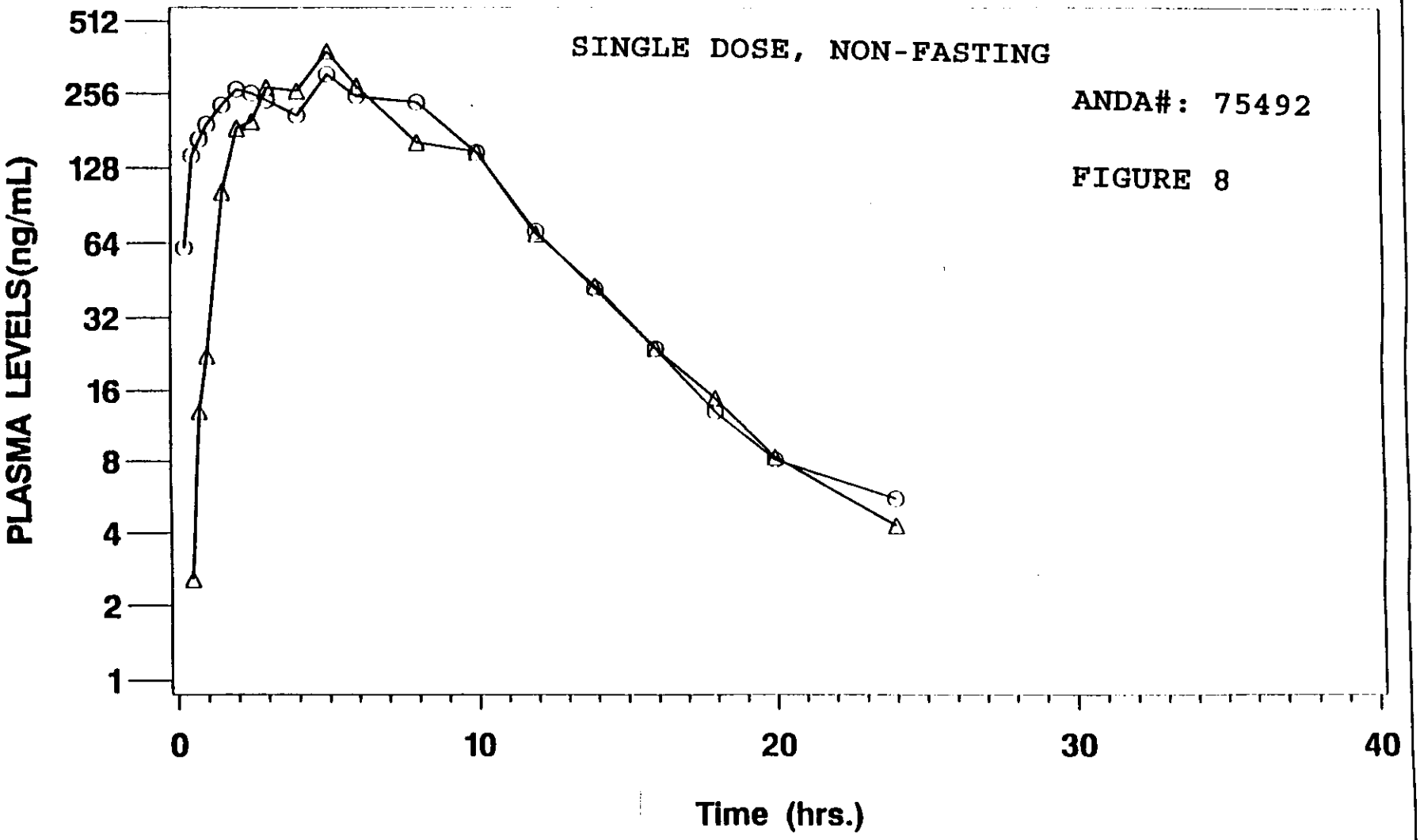
MEAN PLASMA DICLOFENAC CONCENTRATIONS

(STUDY # 1957 – 1)



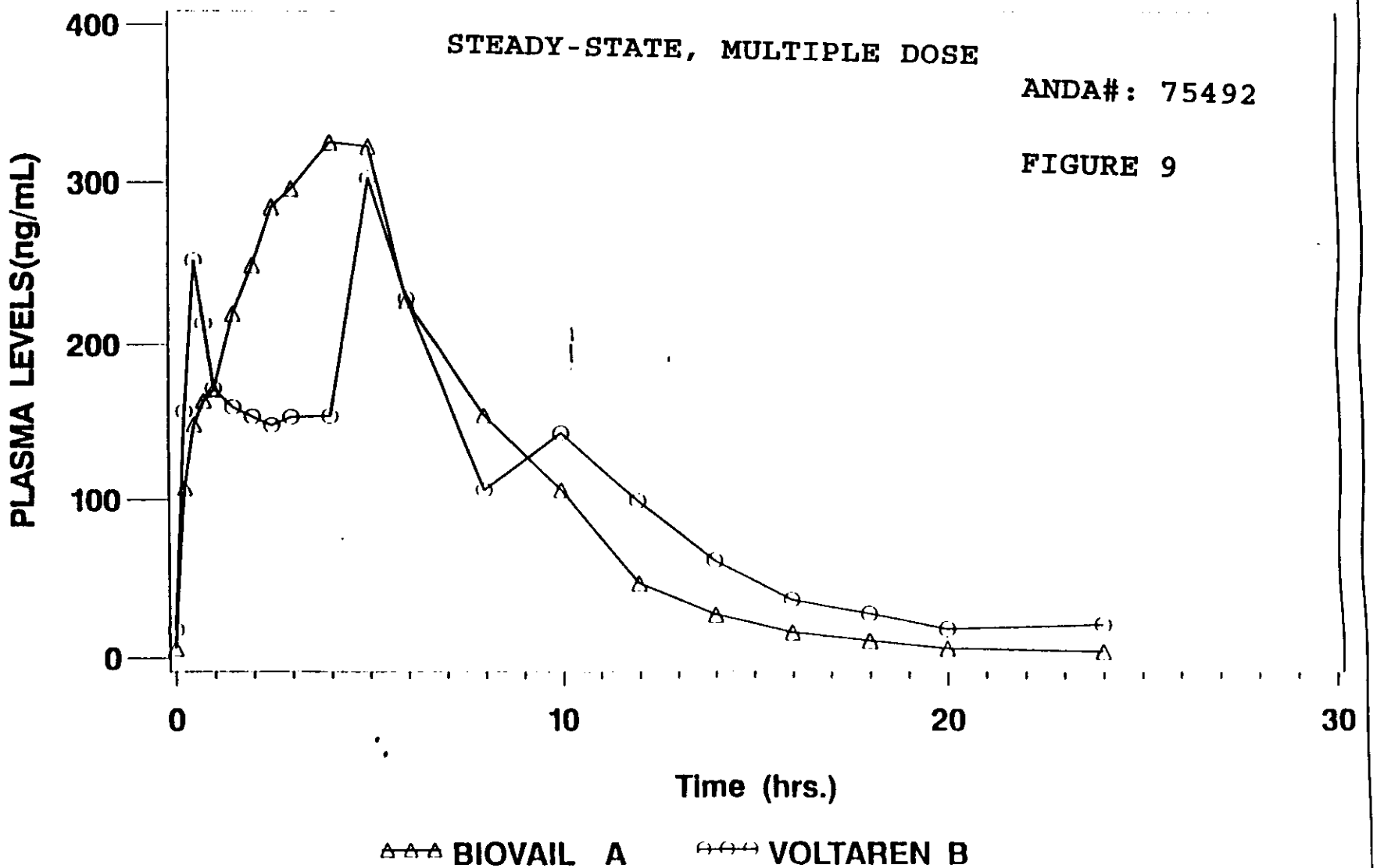
SEMI LOG MEAN PLASMA DICLOFENAC CONCENTRATIONS

(STUDY # 1957 – 1)



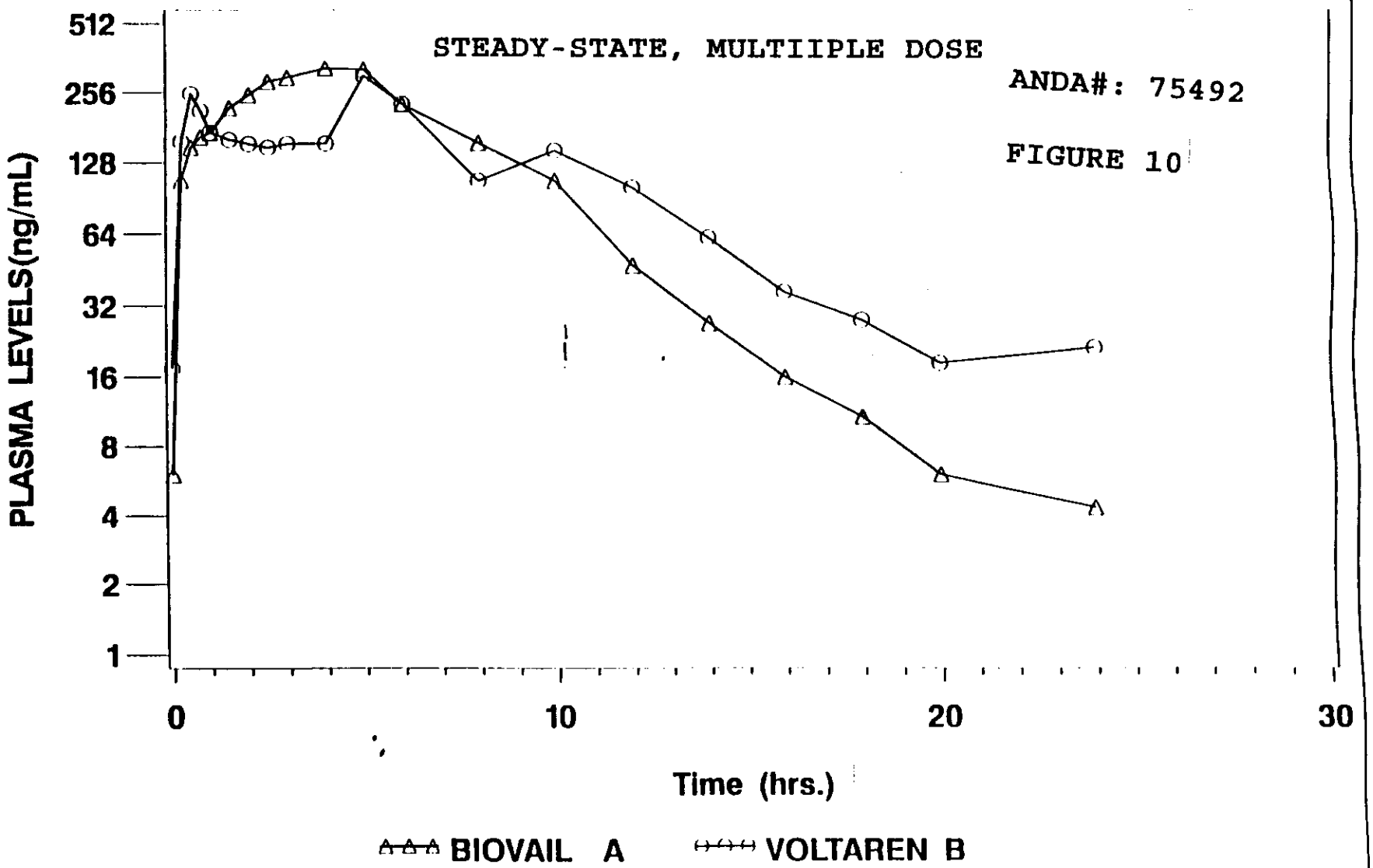
MEAN PLASMA DICLOFENAC CONCENTRATIONS

(STUDY # 2011) (DAY 7)



SEMI LOG MEAN PLASMA DICLOFENAC CONCENTRATIONS

(STUDY # 2011) (DAY 7)



5132

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-492 APPLICANT: BIOAVAIL LABS.

DRUG PRODUCT: DICLOFENAC SODIUM EXTENDED RELEASE TABLETS 100MG

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.5, at 37°C using USP Apparatus II(paddle) at 50 rpm. The test product should meet the following interim specifications:

Time(hours)	**% Dissolved**

The firm should also note the following comments for future submissions:

1. The elimination rate constant(Kel) should be calculated using a minimum of 3-time points.

2. The data in firm's diskette should read exactly the same as provided in hard copy. For instance, the AUC_{TAU} on the diskette was over 8 hours whereas the actual period was up to 24 hours.

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,

/S/

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

BIOEQUIVALENCY - ACCEPTABLE submission date: October 30, 1998

1. **FASTING STUDY** (STF) Strengths: 100MG _____
   Clinical: BIOAVAIL **Outcome:** **AC**
   Analytical: BIOAVAIL _____

2. **FOOD STUDY** (STP) Strengths: 100MG
   Clinical: BIOAVAIL **Outcome:** **AC**
   Analytical: BIOAVAIL _____

3. **MULTIPLE DOSE STUDY** (STM) Strengths: 100MG
   Clinical: BIOAVAIL **Outcome:** **AC**
   Analytical:BIOAVAIL _____

~~4. **DISSOLUTION DATA** (DIS) **Outcome:** **AC**~~

Outcome Decisions: **AC** - Acceptable

WinBio Comments: STF - Acceptable
STP - Acceptable
STM - Acceptable
Dissolution - Acceptable

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-492

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 75-492 **Date of Submission: October 30, 1998**

Applicant's Name: Keller & Heckman

Established Name: Diclofenac Sodium Extended-release Tablets, 100 mg

Labeling Deficiencies:

1. CONTAINER (100's, 500's, and 1000's)

   Increase the prominence and conspicuousness of "100 mg" in the established name.

2. INSERT

   a. TITLE

      We encourage the inclusion of "℞ only" in this section.

   b. DESCRIPTION
      Revise the second paragraph of this section to read as follows:

      Diclofenac is a faintly yellowish white to light beige virtually odorless, slightly hygroscopic crystalline powder. The molecular weight of diclofenac sodium is 318.14. It is freely soluble in methanol, soluble in ethanol, and practically insoluble in chloroform and in dilute acid. Diclofenac sodium is sparingly soluble in water. The n-octanol/water...

   c. CLINICAL PHARMACOLOGY-Pharmacokinetics (Table 1)

      We defer comment pending review of the Bioequivalence study.

Please revise your container labels and insert labeling, as instructed above, and submit 12 copies of final printed container labels for each package size, along with 12 copies of final printed insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

/S/

Robert L. West, M.S., R.Ph.
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 75-492

CORRESPONDENCE

BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL

OVERNIGHT COURIER
MINOR AMENDMENT

November 19, 1999

ORIG AMENDMENT
N/AM

Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Diclofenac Sodium Extended-release Tablets, 100 mg
Response to a Minor Amendment of November 10, 1999
ANDA # 75-492

Dear Mr. Sporn,

Biovail Laboratories Inc. wishes to amend its application, ANDA # 75-492, to include responses to the Agency correspondence of November 10, 1999.

Biovail has addressed all questions and comments posed by the Agency.

In addition, Biovail Laboratories Inc. wishes to notify the agency that resin used in manufacture of 80cc bottles, and . resin used in manufacture of 400cc and 750cc bottles, will no longer be used. resin, submitted in the original ANDA application as an alternate resin, will be used for manufacture of all bottle sizes. Comparative USP <671> testing, demonstrating equivalence of the resins, was submitted in the original application.

We look forward to receiving Agency comment on this amendment, if any, in due course.

If you have any questions or comments, please contact me at telephone number (416) 285-6000, extension 219 or, at fax number (905) 608-1616.

Yours respectfully,
BIOVAIL CORPORATION INTERNATIONAL

NOV 1999

Wayne Kreppner, M.Sc.,
Manager, Corporate Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

11-19

BIOVAIL CORPORATION INTERNATIONAL
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

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OVERNIGHT COURIER
MAJOR AMENDMENT

June 1, 1999

Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AC

RE: Diclofenac Sodium Extended-release Tablets, 100 mg
Response to a Major Amendment of May 4, 1999
ANDA # 75-492

Dear Mr. Sporn,

Biovail Laboratories Inc. wishes to amend its application, ANDA # 75-492, to include responses to the Agency correspondence of May 4, 1999.

Biovail has addressed all questions and comments posed by the Agency. In particular, the applicant has amended the dissolution test method and specifications to incorporate the recommendations put forth by the Division of Bioequivalence. Our amendment also includes appendices containing updated Master Batch Records (Appendix I) and updated stability data for the exhibit batch (Appendix II).

We look forward to receiving Agency comment on our responses, if any, in due course.

If you have any questions or comments, please contact me at telephone number (416) 285-6000, extension 219 or, at fax number (905) 608-1616.

Yours respectfully,
BIOVAIL CORPORATION INTERNATIONAL

Wayne Kreppner, M.Sc.,
Manager, Corporate Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

CENTER FOR DRUG
RECD
JUN 02 1999
OGD
EVALUATION AND RESEARCH

Encl.

BIOVAIL CORPORATION INTERNATIONAL
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

ANDA 75-492

Keller & Heckman
Attention: John Dubeck
U.S. Agent for: Biovail Laboratories Inc.
1001 G Street N.W.
Suite 500 West
Washington, DC 20001

NOV 27 1998

Dear Sir:

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

Reference is made to the telephone conversation dated November 12, 1998 and your correspondence dated November 12, 1998.

NAME OF DRUG: Diclofenac Sodium Extended-release Tablets, 100 mg

DATE OF APPLICATION: October 30, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 2, 1998

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:

Pat Beers-Block
Project Manager
(301) 827-5848

Sincerely yours,

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

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OVERNIGHT COURIER

October 30, 1998

Douglas Sporn
Director, Office of Generic Drugs (HFD-110)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application
Diclofenac Sodium Extended-release Tablets, 100mg

Dear Mr. Sporn,

Please find enclosed an Abbreviated New Drug Application for Diclofenac Sodium Extended-release Tablets, 100 mg. This Abbreviated New Drug Application has been prepared as outlined in section 314.94 of 21 CFR and is submitted based on the provisions of 505(j) of the Federal Food, Drug and Cosmetic Act by the sponsor and ANDA holder Biovail Laboratories Incorporated.

Biovail Laboratories Incorporated (BLI), Puerto Rico, is a wholly owned-subsidiary of Biovail Corporation International (BCI). Further to written communications by Mr. Levy, our Manager of Corporate Regulatory Affairs, John Dubeck, Keller and Heckman, is the US Agent for this application.

RECEIVED

NOV 02 1998

CENTER DRUGS

BIOVAIL CORPORATION INTERNATIONAL

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OVERNIGHT COURIER

02 November 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II, HFD-615
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ATTN: Peter Rickman
Chief, Regulatory Support Branch

Re: Diclofenac Sodium Extended-release Tablets, 100 mg

Dear Mr. Rickman,

In reviewing the documents submitted on October 30, 1998, in support of our Abbreviated New Drug Application for Diclofenac Sodium Extended-release Tablets, 100 mg, it was observed that the Debarment Certification, required under section 306 (k) of the Federal Food, Drug and Cosmetic Act, was omitted from Volume 1.

In correction of this oversight one (1) original and three (3) copies of the Debarment Certification have been enclosed for inclusion in our submitted dossier.

If you have any questions or comments, please contact me directly at telephone number (416)285-6000 extension 213 or at fax number (905) 608-1616.

Kindest regards,
ON BEHALF OF BIOVAIL LABORATORIES INCORPORATED

per:

Martin Levy, FBIRA
Manager, Corporate Regulatory Affairs
Biovail Corporation International

Encl.