CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74464

Trade Name Indomethacin Extended-release Capsules USP 75mg

Generic Name Indomethacin Extended-release Capsules USP 75mg

Sponsor Eon Labs Manufacturing, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74464

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Application Number 74464

APPROVAL LETTER

ANDA 74-464 MAY 28

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, N.Y. 11413

Dear Madam:

This is in reference to your abbreviated new drug application dated February 2, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Indomethacin Extended-release Capsules USP, 75 mg.

Reference is also made to your amendments dated October 24, 1995; and March 4, April 6, and April 13, 1998.

Your application contains a patent certification to patent 4,173,626 under Section 505(j)(2)(A)(vii)(IV) of the Act. Section 505(j)(4)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that Eon Labs Manufacturing, Inc. has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Eon Labs Manufacturing, Inc. within the statutory forty-five day period.

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 Indomethacin Extended-release Capsules USP, 75 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Indocin SR Capsules, 75 mg of Merck Research Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-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,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74464

FINAL PRINTED LABELING

Lot No.:
Exp. Date:

USUAL ADULT DOSAGE: See accompanying literature.

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

Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 12/93

NDC 0185-0720-60

Indomethacin Extended-release Capsules, USP

Each capsule contains:
Indomethacin ..... 75 mg

APPROVED

CAUTION: Federal law prohibits dispensing without prescription.

60 Capsules

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0720-60 6

Eon Labs

Lot No.:
Exp. Date:

USUAL ADULT DOSAGE: See accompanying literature.

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

Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 12/93

NDC 0185-0720-01

Indomethacin Extended-release Capsules, USP

Each capsule contains:
Indomethacin ..... 75 mg

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

APPROVED

CAUTION: Federal law prohibits dispensing without prescription.

100 Capsules

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0720-01 9

Eon Labs

Lot No.:
Exp. Date:

USUAL ADULT DOSAGE: See accompanying literature .

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

Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 12/93

NDC 0185-0720-05

Indomethacin Extended-release Capsules, USP

Each capsule contains:
Indomethacin ..... 75 mg

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

CAUTION: Federal law prohibits dispensing without prescription.

500 Capsules

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0720-05 7

Eon Labs

Lot No.:
Exp. Date:

USUAL ADULT DOSAGE: See accompanying literature.

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

Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 12/93

NDC 0185-0720-10

Indomethacin Extended-release Capsules, USP

Each capsule contains:
Indomethacin ..... 75 mg

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

APPROVED

CAUTION: Federal law prohibits dispensing without prescription.

1000 Capsules

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0720-10 1

Eon Labs

APPROVED

MAY 28 1996

INDOMETHACIN EXTENDED-RELEASE CAPSULES, USP 75 mg

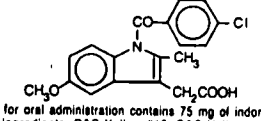
0720

INDOMETHACIN EXTENDED-RELEASE CAPSULES, USP 75 mg

DESCRIPTION:

Indomethacin cannot be considered a simple analgesic and should not be used in conditions other than those recommended under **INDICATIONS AND USAGE.**

Indomethacin is a nonsteroidal, anti-inflammatory, indole derivative designated chemically as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid. Indomethacin is practically insoluble in water and sparingly soluble in alcohol. It has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali. The structural formula is:



M.W. 357.80 $C_{19}H_{16}ClNO_4$

Each extended-release capsule, for oral administration contains 75 mg of indomethacin. In addition, each capsule contains the following inactive ingredients: D&C Yellow #10, D&C Yellow #10 Aluminum Lake, FD&C Blue #1 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake, FD&C Green #3, ethylcellulose, gelatin, lactose monohydrate, povidone, silicon dioxide, sodium lauryl sulfate, corn starch, sucrose, talc, and titanium dioxide.

This product meets USP Drug Release Test 2 Specifications.

CLINICAL PHARMACOLOGY:

Indomethacin is a nonsteroidal drug with anti-inflammatory, antipyretic and analgesic properties. Its mode of action, like that of other anti-inflammatory drugs, is not known. However, its therapeutic action is not due to pituitary-adrenal stimulation.

Indomethacin is a potent inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy which have been demonstrated to have an effect *in vivo* as well. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Moreover, prostaglandins are known to be among the mediators of inflammation. Since indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Indomethacin has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

Indomethacin affords relief of symptoms; it does not alter the progressive course of the underlying disease.

Indomethacin suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with indomethacin for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength.

Indomethacin has been reported to diminish basal and CO_2 stimulated cerebral blood flow in healthy volunteers following acute oral and intravenous administration. In one study, after one week of treatment with orally administered indomethacin, this effect on basal cerebral blood flow had disappeared. The clinical significance of this effect has not been established.

Indomethacin Extended-release Capsules (75 mg) are designed to release 25 mg of drug initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours). Plasma concentrations of indomethacin fluctuate less and are more sustained following administration of Indomethacin Extended-release Capsules than following administration of 25 mg indomethacin capsules given at 4 to 6 hour intervals. In multiple-dose comparisons, the mean daily steady state plasma level of indomethacin attained with daily administration of Indomethacin Extended-release Capsules 75 mg was indistinguishable from that following indomethacin 25 mg capsules given at 0, 6, and 12 hours daily. However, there was a significant difference in indomethacin plasma levels between the two dosage regimens especially after 12 hours.

Controlled clinical studies of safety and efficacy in patients with osteoarthritis have shown that one capsule of Indomethacin Extended-release was clinically comparable to one 25 mg indomethacin capsule t.i.d.; and in controlled clinical studies in patients with rheumatoid arthritis, one capsule of Indomethacin Extended-release taken in the morning and one in the evening were clinically indistinguishable from one 50 mg capsule of indomethacin t.i.d.

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean half-life of indomethacin is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 or 50 mg t.i.d., the steady state plasma concentrations of indomethacin are an average 1.4 times those following the first dose.

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60 percent of an oral dosage is recovered in urine as drug and metabolites (26 percent as indomethacin and its glucuronide), and 33 percent is recovered in feces (1.5 percent as indomethacin).

About 99% of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta.

INDICATIONS AND USAGE:

Indomethacin Extended-release Capsules have been found effective in active stages of the following:

1. Moderate to severe rheumatoid arthritis including acute flares of chronic disease.
2. Moderate to severe ankylosing spondylitis.
3. Moderate to severe osteoarthritis.
4. Acute painful shoulder (bursitis and/or tendinitis).

Indomethacin Extended-release Capsules are not recommended for the treatment of acute gouty arthritis.

Indomethacin may enable the reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis. In such instances the steroid dosage should be reduced slowly and the patients followed very closely for any possible adverse effects.

The use of indomethacin in conjunction with aspirin or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of indomethacin and aspirin does not produce any greater therapeutic effect than the use of indomethacin alone. Furthermore, in one of these clinical studies, the incidence of gastrointestinal side effects was significantly increased with combined therapy. (See **PRECAUTIONS, Drug Interactions**).

CONTRAINDICATIONS:

Indomethacin should not be used in:

Patients who are hypersensitive to this product.

Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other nonsteroidal anti-inflammatory agents.

WARNINGS:

General: Because of the variability of the potential of indomethacin to cause adverse reactions in the individual patient, the following are strongly recommended:

1. The lowest possible effective dose for the individual patient should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150-200 mg/day, without corresponding increase in clinical benefits.
2. Careful instructions to, and observations of, the individual patient are essential to the prevention of serious adverse reactions. As advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the aged.
3. Effectiveness of indomethacin in children has not been established. Indomethacin should not be prescribed for children 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk.

   In experience with more than 900 children reported in the literature or elsewhere who were treated with indomethacin capsules, side effects in children were comparable to those reported in adults. Experience in children has been confined to the use of indomethacin capsules.

   If a decision is made to use indomethacin for children two years of age or older, such patients should be monitored closely and periodic assessment of liver function is recommended. There have been cases of hepatotoxicity reported in children with juvenile rheumatoid arthritis, including fatalities.

   If indomethacin treatment is instituted, a suggested starting dose is 2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 4 mg/kg/day or 150-200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level required to control symptoms, or the drug should be discontinued.
4. If Indomethacin Extended-release Capsules are used for initial therapy or during dosage adjustment, observe the patient closely (See **DOSAGE AND ADMINISTRATION**).

Gastrointestinal Effects: Single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestine, have been reported to occur with indomethacin. Fatalities have been reported in some instances. Rarely, intestinal ulceration has been associated with stenosis and obstruction.

Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred. Increased abdominal pain in ulcerative colitis patients or the development of ulcerative colitis and regional ileitis have been reported to occur rarely.

Because of the occurrence, and at times severity, of gastrointestinal reactions to indomethacin, the prescribing physician must be continuously alert for any sign or symptom signaling a possible gastrointestinal reaction. The risks of continuing therapy with indomethacin in the face of such symptoms must be weighed against the possible benefits to the individual patient.

Indomethacin should not be given to patients with active gastrointestinal lesions or with a history of recurrent gastrointestinal lesions except under circumstances which warrant the very high risk and where patients can be monitored very closely.

The gastrointestinal effects may be reduced by giving the indomethacin immediately after meals, with food, or with antacids.

Risk of GI 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 GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

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

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

A second form of renal toxicity has been seen in patients with prerenal and renal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a NSAID may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with conditions such as renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion from any cause, congestive heart failure, septicemia, pyelonephritis, or concomitant use of any nephrotoxic drug. Indomethacin or other NSAIDs should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Increases in serum potassium concentration, including hyperkalemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state (See **PRECAUTIONS, Drug Interactions**).

Since indomethacin is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be anticipated to avoid excessive drug accumulation.

Ocular Effects: Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with indomethacin. The prescribing physician should be alert to the possible association between the changes noted and indomethacin. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmological examination at periodic intervals is desirable in patients where therapy is prolonged.

Central Nervous System Effects: Indomethacin may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. If severe CNS adverse reactions develop, indomethacin should be discontinued.

Indomethacin may cause drowsiness; therefore, patients should be cautioned about engaging in activities requiring mental alertness and motor coordination, such as driving a car. Indomethacin may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with indomethacin.

Use in Pregnancy and the Neonatal Period: Indomethacin is not recommended for use in pregnant women, since safety for use has not been established, and because of the known effect of drugs of this class on the human fetus (closure of the ductus arteriosus, platelet dysfunction with resultant bleeding, renal dysfunction or failure with oligohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes) during the third trimester of pregnancy.

Teratogenic studies were conducted in mice and rats at dosages of 0.5, 1, 2, and 4 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day considered secondary to the decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. Comparable studies in rodents using high doses of aspirin have shown similar maternal and fetal effects.

As with other nonsteroidal anti-inflammatory agents which inhibit prostaglandin synthesis, indomethacin has been found to delay parturition in rats.

In rats and mice, 4 mg/kg/day given during the last three days of gestation caused a decrease in maternal weight gain and some maternal and fetal deaths. An increased incidence of neuronal necrosis in the diencephalon in the five-born fetuses was observed. At 2 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups. Administration of 0.5 or 4 mg/kg/day during the first three days of life did not cause an increase in neuronal necrosis at either dose level.

Use in Nursing Mothers: Indomethacin is excreted in the milk of lactating mothers. Indomethacin is not recommended for use in nursing mothers.

PRECAUTIONS:

General: Nonsteroidal, anti-inflammatory drugs, including indomethacin, may mask the usual signs and symptoms of existing infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing infection.

Fluid retention and peripheral edema have been observed in some patients taking indomethacin. Therefore, as with other nonsteroidal, anti-inflammatory drugs, indomethacin should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions predisposing to fluid retention.

In a study of patients with severe heart failure and hyponatremia, indomethacin was associated with significant deterioration of circulatory hemodynamics, presumably due to inhibition of prostaglandin dependent compensatory mechanisms.

Indomethacin, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation. This effect is of shorter duration than that seen with aspirin and usually disappears within 24 hours after discontinuation of indomethacin. Indomethacin has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this effect may be exaggerated in patients with underlying hemostatic defects, indomethacin should be used with caution in persons with coagulation defects.

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

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

NSAIDS (Nonsteroidal Anti-Inflammatory Drugs) are often essential agents in the management of arthritis; but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS** sections) and likely benefits of 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.

Laboratory Tests: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see **WARNINGS, Risk of GI Ulcerations, Bleeding and Perforation with NSAID therapy**).

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day, indomethacin had no tumorigenic effect.

Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73-110 weeks) and the mouse (dosing period 62-88 weeks) at doses up to 1.5 mg/kg/day.

Indomethacin did not have any mutagenic effect in *in vitro* bacterial tests (Ames test and *E. Coli* with or without metabolic activation) and a series of *in vivo* tests including the host-mediated assay, sex-linked recessive lethals in *Drosophila*, and the micronucleus test in mice.

Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study or a two litter reproduction study in rats.

Drug Interactions: In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, diflunisal and indomethacin should not be used concomitantly.

In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin blood levels approximately 20%.

Clinical studies have shown that indomethacin does not influence the hypoprothrombinemia produced by anticoagulants. However, when any additional drug, including indomethacin, is added to the treatment of patients on anti coagulant therapy, the patients should be observed for alterations of the prothrombin time.

When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, a lower total daily dosage of indomethacin may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin are made, they should be made carefully and in small increments.

Caution should be used if indomethacin is administered simultaneously with methotrexate. Indomethacin has been reported to decrease the tubular secretion of methotrexate and to potentiate its toxicity.

Administration of nonsteroidal anti-inflammatory drugs concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporine, and renal function should be carefully monitored.

Indomethacin capsules, 50 mg t.i.d. produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when indomethacin and lithium are given concomitantly, the patient should be carefully observed for signs of lithium toxicity. (Read circulars for lithium preparations before use of such concomitant therapy.) In addition, the frequency of monitoring serum lithium concentration should be increased at the outset of such combination drug treatment.

Indomethacin given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when indomethacin and digoxin are used concomitantly, serum digoxin levels should be monitored closely.

In some patients, the administration of indomethacin can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when indomethacin and diuretics are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together.

Indomethacin and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by indomethacin.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs including indomethacin has been reported. Therefore, when using these blocking agents to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained. There are reports that indomethacin can reduce the antihypertensive effect of captopril in some patients.

False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

Pediatric Use: Effectiveness in children 14 years of age and younger has not been established (See WARNINGS).

ADVERSE REACTIONS:

The adverse reactions for indomethacin capsules listed in the following table have been arranged into two groups: 1) incidence greater than 1% and (2) incidence less than 1%. The incidence for group (1) was obtained from 33 double-blind controlled clinical trials reported in the literature (1,092 patients). The incidence for group (2) was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between indomethacin and these adverse reactions, some of which have been reported only rarely.

In controlled clinical trials, the incidence of adverse reactions to Indomethacin Extended-release Capsules and equal 24-hour doses of indomethacin capsules were similar.

Incidence greater than 1%	Incidence less than 1%	
GASTROINTESTINAL		
nausea* with or without vomiting dyspepsia* (including indigestion, heartburn and epigastric pain) diarrhea abdominal distress or pain constipation	anorexia bloating (includes distention) flatulence peptic ulcer gastroenteritis rectal bleeding proctitis single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines intestinal ulceration associated with stenosis and obstruction	gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) development of ulcerative colitis and regional ileitis ulcerative stomatitis toxic hepatitis and jaundice (some fatal cases have been reported)
CENTRAL NERVOUS SYSTEM		
headache (11.7%) dizziness* vertigo somnolence depression and fatigue (including malaise and listlessness)	anxiety (includes nervousness) muscle weakness involuntary muscle movements insomnia muzziness psychic disturbances including psychotic episodes mental confusion drowsiness	light-headedness syncope paresthesia aggravation of epilepsy and parkinsonism depersonalization coma peripheral neuropathy convulsions dysarthria
SPECIAL SENSES		
tinnitus	ocular-corneal deposits and retinal disturbances, including those of macula, have been reported in some patients on prolonged therapy with indomethacin	blurred vision diplopia hearing disturbances, deafness
CARDIOVASCULAR		
none	hypertension hypotension tachycardia chest pain	congestive heart failure arrhythmia; palpitations
METABOLIC		
none	edema weight gain fluid retention flushing or sweating	hyperglycemia glycosuria hyperkalemia
INTEGUMENTARY		
none	pruritus rash; urticaria petechiae or ecchymosis	exfoliative dermatitis erythema nodosum loss of hair Stevens-Johnson syndrome erythema multiforme toxic epidermal necrolysis
HEMATOLOGIC		
none	leukopenia bone marrow depression anemia secondary to obvious or occult gastrointestinal bleeding	aplastic anemia hemolytic anemia agranulocytosis thrombocytopenic purpura disseminated intravascular coagulation
HYPERSENSITIVITY		
none	acute anaphylaxis acute respiratory distress rapid fall in blood pressure resembling a shock-like state angioedema	dyspnea asthma purpura angiitis pulmonary edema fever
GENITOURINARY		
none	hematuria vaginal bleeding proteinuria nephrotic syndrome interstitial nephritis	BUN elevation renal insufficiency including renal failure
MISCELLANEOUS		
none	epistaxis breast changes, including enlargement and tenderness, or gynecomastia	

* Reactions occurring in 3% to 9% of patients treated with indomethacin. (Those reactions occurring in less than 3% of the patients are unmarked.)

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

A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A β-hemolytic streptococcus, has been described in persons treated with nonsteroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcome (see also PRECAUTIONS, General).

Cardiovascular: Thrombophlebitis.
Hematologic: Although there have been several reports of leukemia, the supporting information is weak.
Genitourinary: Urinary frequency.

OVERDOSAGE:

The following symptoms may be observed following overdosage: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy. There have been reports of paresthesias, numbness, and convulsions.

Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible if the ingestion is recent. If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac. If the patient is unable to vomit, gastric lavage should be performed. Once the stomach has been emptied, 25 or 50 g of activated charcoal may be given. Depending on the condition of the patient, close medical observation and nursing care may be required. The patient should be followed for several days because gastrointestinal ulceration and hemorrhage have been reported as adverse reactions of indomethacin. Use of antacids may be helpful.

The oral LD_{50} of indomethacin in mice and rats (based on 14 day mortality response) was 50 and 12 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:

Indomethacin Extended-release Capsules 75 mg are available for oral use. Indomethacin Extended-release Capsules can be administered once a day and can be substituted for indomethacin 25 mg capsules t.i.d. However, there will be significant differences between the two dosage regimens in indomethacin blood levels, especially after 12 hours (see CLINICAL PHARMACOLOGY). In addition, Indomethacin Extended-release Capsules 75 mg b.i.d. can be substituted for indomethacin 50 mg capsules t.i.d. Indomethacin Extended-release Capsules may be substituted for all the indications of indomethacin capsules except acute gouty arthritis.

Adverse reactions appear to correlate with the size of the dose of indomethacin in most patients, but not all. Therefore, every effort should be made to determine the smallest effective dosage for the individual patient.

Always give Indomethacin Extended-release Capsules 75 mg with food, immediately after meals, or with antacids to reduce gastric irritation.

Pediatric Use: Indomethacin ordinarily should not be prescribed for children 14 years of age and under (see WARNINGS).

Adult Use: Dosage Recommendations for Active Stages of the Following:

1. Moderate to severe rheumatoid arthritis, including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis.

The following information is provided as background only and refers to immediate-release indomethacin capsules (25 mg or 50 mg):

Suggested Dosage:

The following recommendations on dosing pertain to immediate-release indomethacin capsules USP, and provide important information regarding the dosage and administration of indomethacin. The prescriber should be aware of this information when considering and prescribing extended-release indomethacin.

Indomethacin capsules 25 mg b.i.d. or t.i.d. If this is well tolerated, increase the daily dosage by 25 or 50 mg, if required by continuing symptoms, at weekly intervals until a satisfactory response is obtained or until a total daily dose of 150-200 mg is reached. DOSES ABOVE THIS AMOUNT GENERALLY DO NOT INCREASE THE EFFECTIVENESS OF THE DRUG.

In patients who have persistent night pain and/or morning stiffness, the giving of a large portion, up to a maximum of 100 mg, of the total daily dose at bedtime, either orally or by rectal suppositories, may be helpful in affording relief. The total daily dose should not exceed 200 mg. In acute flares of chronic rheumatoid arthritis, it may be necessary to increase the dosage by 25 mg or, if required, by 50 mg daily.

The following information refers to Extended-release Indomethacin Capsules (75 mg):

If Indomethacin Extended-release Capsules are used for initiating indomethacin treatment, one capsule daily should be the usual starting dose in order to observe patient tolerance since 75 mg per day is the maximum recommended starting dose for indomethacin (see above). If Indomethacin Extended-release Capsules are used to increase the daily dose, patients should be observed for possible signs and symptoms of intolerance since the daily increment will exceed the daily increment recommended for other dosage forms. For patients who require 150 mg of Indomethacin per day and have demonstrated acceptable tolerance, Indomethacin Extended-release Capsules 75 mg may be prescribed as one capsule twice daily.

If minor adverse effects develop as the dosage is increased, reduce the dosage rapidly to a tolerated dose and OBSERVE THE PATIENT CLOSELY.

If severe adverse reactions occur, STOP THE DRUG. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is receiving the smallest effective dose or the drug is discontinued.

Careful instructions to, and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions.

As advancing years appear to increase the possibility of adverse reactions, Indomethacin Extended-release Capsules should be used with greater care in the aged.

2. Acute painful shoulder (bursitis and/or tendinitis). Initial Dose: 75 mg to 150 mg daily. When 150 mg is prescribed, give as one capsule twice daily.

The drug should be discontinued after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7 to 14 days.

HOW SUPPLIED:

Indomethacin Extended-release Capsules 75 mg are supplied as green and clear capsules imprinted Æ 720 and are available in bottles of 60 (as unit of use), 100, 500 and 1000 capsules.

Caution: Federal law prohibits dispensing without prescription.

Storage: Store at controlled room temperature 15° - 30°C (59° - 86°F). Protect from moisture.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

Rev. 2/98
MF0720REV0298
Fist #11782

INDOMETHACIN EXTENDED-RELEASE CAPSULES, USP 75 mg

0720

INDOMETHACIN EXTENDED-RELEASE CAPSULES, USP 75 mg

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74464

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO **7** 2. ANDA **74-464**

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc., Attention: Zohra E. Lomri
227-15 North Conduit Avenue, Laurelton, NY 11413

4. LEGAL BASIS Indocin SR®;Merck SD
patent 4,173,626 expires on 12-11-98 and Merck has certified that Eon is not infringing on this patent (see NC dated 04-06/13-98)

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

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Indomethacin Extended-release Capsules USP

9. AMENDMENTS AND OTHER DATES:

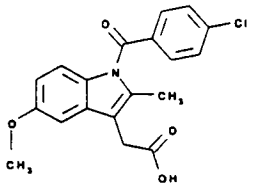
February 2, 1994	Date of application
January 10, 1995	CMC/label NA letter
June 28, 1995	CMC amendment
October 24, 1995	NC bio
July 5, 1996	Bio Acceptable
April 8, 1996	CMC Amendment
December 16, 1996	CMC Major Amendment
August 20, 1997	CMC Minor Amendment
November 20, 1997	CMC Minor Amendment
March 5, 1998	**CMC Minor Amendment - this review**
April 6, 1998	New Correspondence - Patent information
April 13, 1998	New Correspondence - Patent Information

10. PHARMACOLOGICAL CATEGORY NSAID 11. Rx or OTC Rx

12. RELATED NDA/DMFs NDA 18-185

13. DOSAGE FORM oral, hard shell capsule 14. POTENCY **75 mg**

15. CHEMICAL NAME AND STRUCTURE Indomethacin USP
$C_{19}H_{16}ClNO_4$; M.W. = 357.79, CAS [53-86-1]
1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid



16. RECORDS AND REPORTS N/A

17. COMMENTS none

18. CONCLUSIONS AND RECOMMENDATIONS **approve**

19. REVIEWER Melissa Maust DATE COMPLETED April 1, 1998
Updated: April 29, 1998

cc: ANDA 74-464
DUP Jacket
Division File

Endorsements:
HFD-623/M. Maust/ -29-98 5/4/98
HFD-623/V. Sayeed, Ph.D./

Y:\NEW\FIRMSAM\EON\LTRS&REV\74464AP.498
F/T by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74464

BIOEQUIVALENCE REVIEW(S)

ANDA 74-464

Eon Labs Manufacturing Inc.
Attention: John Purpura
227-15 North Conduit Avenue
Laurelton NY 11413

JUL 5 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Indomethacin Extended-Release Capsules USP, 75 mg.

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

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

   The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 6.2 at 37°C using USP 23 apparatus 1 (Basket) at 75 rpm. The test should meet the following specifications:

TIME (hours)	AMOUNT DISSOLVED
1	
2	
4	
12	

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

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 28 1996

Indomethacin ER
75 mg Capsules
ANDA # 74-464
Reviewer: Man M. Kochhar

Eon Labs Manufacturing Inc.
Laurelton, NY
Submission Date:
October 24, 1995

RESPONSE TO DEFICIENCY LETTER

The sponsor has responded to the deficiency letter of October 12, 1995.

ANALYTICAL

1. With the original submission, the percent recovery was given but no data were provided. The data for stability at room temperature and long term stability and freeze-thaw was not given.

NON-FASTING

The sponsor has provided the log transformed data and is acceptable to the Division of Bioequivalence.

MULTIPLE-DOSE STUDY

1. All 24 subjects completed the study. The plasma samples from subject 21 and 22 were unacceptable. The sponsor did not provide any reason for unacceptable data.

The sponsor has provided the r subject 21 and 22. All data for subjects 21 and 22 were omitted from the data base included in the pharmacokinetic and statistical analysis. The original assay from subject 21 was rejected because of

With this study, there were 4 minimum concentrations obtained for each subject treatment: pre-dose on day 2, 3, and 4 and 24 hours after dose 4. This represent 176 minimum concentrations, of which 81 were below the limit of quantitation, and thus were reported as 0.000 mcg/mL in the data base. For both the test and reference formulations, the Newman Keuls a posteriori test indicated that there were no differences (p>0.05) among the four minimum concentrations, demonstrating that steady-state had been reached for both the products.

Newman Keuls a posteriori Test

Ranking of Minimums

Product				
Drug 1 (Reference)	1	3	4	2
Drug 2 (Test)	3	1	4	2

1= Minimum Pre Dose Day 2
2= Minimum Pre Dose Day 3
3= Minimum Pre Dose Day 4
4= Minimum 24 hours Day 4

* Numbers underlined not different (p>0.05)

According to Don, this method is recognized as a valid method and can be used to determine the steady state as long as the same is done for the reference. The sponsor has done this for both test and reference products.

The sponsor's analysis does not detect the case where most subjects are at steady state but few are not at steady state.

DISSOLUTION

The sponsor has conducted dissolution according to USP XXIII specifications and are acceptable to the Division of Bioequivalence.

The response to the deficiency letter is acceptable to the Division of Bioequivalence.

RECOMMENDATIONS:

The fasting, non-fasting and multiple-dose bioequivalence studies conducted by Eon Labs on its Indomethacin Extended Release Capsules, USP 75 mg, lot # 930301, comparing it to Indocin SR capsules, 75 mg, lot # V0621, manufactured by Merck, Sharp & Dohme have been found acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting, non-fasting, and multiple-dose conditions the Eon Lab's Indomethacin ER capsules, 75 mg are bioequivalent to the reference product Indocin SO capsules, 75 mg manufactured by Merck, Sharp & Dome.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 6.2 at 37° C using USP XXIII apparatus 1 (Basket) at 75 rpm. The test should meet the following specifications:

TIME (hours)	AMOUNT DISSOLVED
1	
2	
4	
12	

3. From the bioequivalence point of view, the firm has met the requirements for in vivo and in vitro dissolution testing and the study is acceptable.

Man M. Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRF _____ 6/26/96

Concur: _____ Date: 6/28/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/ 74-464 bio response

cc: ANDA # 74-464 original, HFD-630, HFD-600 (Hare), HFD-344 (Cviswanathan), HFD-658 (Kochhar, Mhatre), Drug File, Division File.

IN VITRO DISSOLUTION TESTING

Drug: Indomethacin ER
Strength: 75 mg
ANDA# 74-464
Firm: Eon Labs
Submission Date: February 2, 1995 and October 24, 1995

Conditions for Dissolution Testing:

USP XXIII, Apparatus 1 (Basket) at 75 RPM
Medium: 900 mL of phosphate buffer, pH 6.2
Specifications: 1 hour
2 hours
4 hours
12 hours

Reference Drug: Indocin SO, 75 mg

RESULTS

Sampling Times (Hours)	Test Product Lot # 930301 Strength 75 mg			Reference Product Lot # VO621 Strength 75 mg		
	Mean	Range	%RSD	Mean	Range	%RSD
1	20.9		8.7	9.6		25.5
2	40.1		7.5	20.7		10.2
4	69.4		6.0	35.8		6.3
12	104.9		3.0	68.4		4.5