

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number **74929**

Trade Name **Etodolac Capsules 300mg**

Generic Name **Etodolac Capsules 300mg**

Sponsor **Aesgen, Inc.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74929

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74929

APPROVAL LETTER

ANDA 74-929

Aesgen Inc.
Attention: Suzanne Yu; U.S. Agent
5051 New Centre Drive
Suite 103
Wilmington, NC 28403

JUL 30 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated July 23, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etodolac Capsules, 300 mg.

Reference is also made to your amendments dated June 23, 1997, August 19, 1997, November 20, 1997 and January 12, 1998.

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

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

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

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

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

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74929

FINAL PRINTED LABELING

Each capsule contains 300 mg etodolac.
USUAL DOSAGE: See package circular for full prescribing information. Dispense in a well-closed container, as defined in the USP.
Store at 15°C - 30°C (59°F - 86°F). Protect from moisture.

Manufactured for:
Aesgen Inc.
Princeton, NJ 08540
By:
MOVA PHARMACEUTICAL CORPORATION
Caguas, P.R. 00725, USA

ETODOLAC
Capsules
300 mg

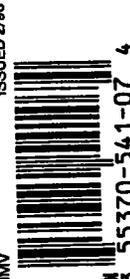
CAUTION: Federal law prohibits dispensing without prescription.

100 Capsules

NDC 55370-541-07

LOT #: 201500
EXP. DATE:

6235200MV



ISSUED 2/96

3 55370-541-07-4

Each capsule contains 300 mg etodolac.
USUAL DOSAGE: See package circular for full prescribing information. Dispense in a well-closed container, as defined in the USP.
Store at 15°C - 30°C (59°F - 86°F). Protect from moisture.

Manufactured for:
Aesgen Inc.
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By:
MOVA PHARMACEUTICAL CORPORATION
Caguas, P.R. 00725, USA

ETODOLAC
Capsules
300 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Capsules

NDC 55370-541-08

LOT #: 201500
EXP. DATE:

6235500MV



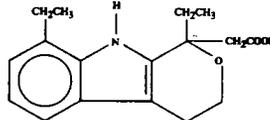
ISSUED 2/96

3 55370-541-08-1

ETODOLAC etodolac capsules and tablets
APPROVED
 635800MV
 JAN 30 1993

DESCRIPTION

Etodolac (etodolac capsules and tablets) is a pyranocarboxylic acid chemically designated as (+) 1,8-diethyl-1,3,4,9-tetrahydropyrido[1,2-b]indole-3-carboxylic acid. The structural formula for etodolac is shown below:



The molecular formula for etodolac is C₂₀H₂₅NO₃. The molecular weight of the base is 287.37. It has a pKa of 4.65 and an n-octanol: water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol. Each tablet, for oral administration, contains 400 mg of etodolac. In addition, the tablets contain the following inactive ingredients: hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide and triacetin.

Each capsule, for oral administration, contains 300 mg of etodolac. In addition, the capsules contain the following inactive ingredients: black iron oxide, gelatin, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium starch glycolate, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacology

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac, like that of other NSAIDs, is not known but is believed to be associated with the inhibition of prostaglandin biosynthesis. Etodolac is a racemic mixture of [-]-R- and [+]-S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the [+]-S-form is biologically active. Both enantiomers are stable and there is no [-]-R to [+]-S conversion *in vivo*.

Pharmacodynamics

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

Pharmacokinetics

The pharmacokinetics of etodolac have been evaluated in 267 normal subjects, 44 elderly patients (>65 years old), 19 patients with renal failure (creatinine clearance 37 to 88 mL/min), 9 patients on hemodialysis, and 10 patients with compensated hepatic cirrhosis.

Etodolac, when administered orally, exhibits kinetics that are well described by a two-compartment model with first-order absorption.

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin, glyburide, furosemide or hydrochlorothiazide.

Absorption

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

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

Kinetic Parameters	Mean ± SD
Extent of oral absorption (bioavailability) [F]	≥ 80%
Oral-dose clearance [CL/F]	47 ± 16 mL/h/kg
Steady-state volume [V _{SS} /F]	362 ± 129 mL/kg
Distribution half-life [t _{1/2, α}]	0.71 ± 0.5 h
Terminal half-life [t _{1/2, β}]	7.3 ± 4 h

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Antacid Effects

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

Food Effects

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

Distribution

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

Metabolism

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

Protein Binding

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

Elimination

The mean plasma clearance of etodolac, following oral dosing is $47 (\pm 16)$ mL/h/kg, and terminal disposition half-life is $7.3 (\pm 4)$ hours.

Approximately 72% of the administered dose is recovered in the urine as the following, indicated as % of the administered dose:

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

Fecal excretion accounted for 16% of the dose.

Special Populations

Elderly Patients

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

Renal Impairment

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

Hepatic Impairment

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

Clinical Trials

Analgesia

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

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Osteoarthritis

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

Risk of Gastrointestinal (GI) Ulceration, Bleeding, and Perforation with Nonsteroidal, Anti-Inflammatory Drug (NSAID) Therapy

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

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

Anaphylactoid Reactions

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

Advanced Renal Disease

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

Pregnancy

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

PRECAUTIONS

General Precautions

Renal Effects

As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study.

A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure or liver dysfunction; those taking diuretics; and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in **ADVERSE REACTIONS**) may be attributable to these metabolites should be considered.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including etodolac. These abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Meaningful elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with etodolac. A patient with symptoms and/or signs suggestive of liver dysfunction, or in whom

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patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of such agents for several months to 2 years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appears to occur in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

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

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Advanced Renal Disease

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

Pregnancy

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

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A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure or liver dysfunction; those taking diuretics; and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in **ADVERSE REACTIONS**) may be attributable to these metabolites should be considered.

Hepatic Effects

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

Hematological Effects

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

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

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

Pre-existing Asthma

About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, etodolac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

Information for Patients

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

Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**) and likely benefits of nonsteroidal anti-inflammatory drug treatment.

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

Because serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this follow-up (see **WARNINGS—Risk of GI Ulceration, Bleeding and Perforation with Nonsteroidal Anti-inflammatory Therapy**).

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

Laboratory Tests

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

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

Drug Interactions

Antacids

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

Aspirin

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

Warfarin

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

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

Phenylbutazone

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

Drug/Laboratory Test Interference

The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose relationship has been observed. Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dL were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m² respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3 to 5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 mcg/ml) compared to negative controls (2%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no

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The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose relationship has been observed. Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dL were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m² respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3 to 5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 mcg/mL) compared to negative controls (2%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m²). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

Pregnancy

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Population

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

ADVERSE REACTIONS

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

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

Incidence Greater Than or Equal to 1% - Probably Causally Related

Body as a whole—Chills and fever.
Digestive system—Dyspepsia (10%), abdominal pain*, diarrhea*, flatulence*, nausea*, constipation, gastritis, melena, vomiting.

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

Skin and appendages—Pruritus, rash.
Special senses—Blurred vision, tinnitus.

Urogenital system—Dysuria, urinary frequency.

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

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

Incidence Less Than 1% - Probably Causally Related

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

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

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

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

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

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

Nervous system—Insomnia, somnolence.

Respiratory system—Asthma.

Clin and ophthalmics—*Angioedema, sweating, urticaria.*

vesiculobullous rash, cutaneous vasculitis with purpura, Stevens-Johnson Syndrome, hyperpigmentation, erythema multiforme.
Special senses—Photophobia, transient visual disturbances.
Urogenital system—Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.
Incidence Less Than 1% - Causal Relationship Unknown (Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians)
Body as a whole—Infection, headache.
Cardiovascular system—Arrhythmias, myocardial infarction, cerebrovascular accident.
Digestive system—Esophagitis with or without stricture or cardiospasm, colitis.
Metabolic and nutritional—Change in weight.
Nervous system—Paresthesia, confusion.
Respiratory system—Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis.
Skin and appendages—Alopecia, maculopapular rash, photosensitivity, skin peeling.
Special senses—Conjunctivitis, deafness, taste perversion.
Urogenital system—Cystitis, hematuria, leukorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities.

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

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

DOSAGE AND ADMINISTRATION
As with other NSAIDs, the lowest dose and longest dosing interval should be sought for each patient. Therefore, after observing the response to initial therapy with etodolac, the dose and frequency should be adjusted to suit an individual patient's needs.
Dosage adjustment of etodolac is generally not required in patients with mild to moderate renal impairment. Etodolac should be used with caution in such patients, because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function. (see **PRECAUTIONS - General Precautions, Renal Effects**).

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

Osteoarthritis
The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis is: 300 mg b.i.d., t.i.d., or 400 mg b.i.d., or 500 mg b.i.d. During long-term administration, the dose of etodolac may be adjusted up or down depending on the clinical response of the patient. A lower dose of 600 mg/day may suffice for long-term administration. In patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. When treating patients with higher doses, the physician should observe sufficient increased clinical benefit to justify the higher dose. Physicians should be aware that doses above 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.
In chronic conditions, a therapeutic response to therapy with etodolac is sometimes seen within one week of therapy, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

HOW SUPPLIED
Etodolac capsules and tablets are available as:
Etodolac Capsules
300 mg capsules (light gray opaque capsule printed in white with "300" and "A06" on opposite sides of the body)
—in bottles of 100, NDC 55370-541-07
—in bottles of 500, NDC 55370-541-08
Store at 15°C-30°C (59°F-86°F), protected from moisture.
Dispense in a well-closed container, as defined in the USP.

Etodolac Tablets
400 mg tablets (white, elliptical shaped, unscored tablet, debossed with "A04" on one side and "400" on the other)
—in bottles of 100, NDC 55370-547-07
—in bottles of 500, NDC 55370-547-08
Store at 15°C-30°C (59°F-86°F).
Store tablets in original container until ready to use.
Dispense in a light resistant container.

Caution: Federal law prohibits dispensing without prescription.

Manufactured for
Aesgen INC
Princeton, NJ 08540
by
MOVA PHARMACEUTICAL CORPORATION
Caguas, PR 00725, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

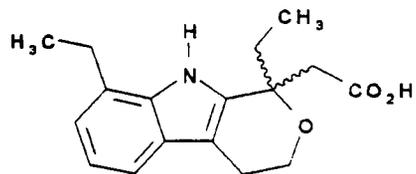
APPLICATION NUMBER 74929

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 3
2. ANDA 74-929
3. NAME AND ADDRESS OF APPLICANT
 Aesgen Inc.
 Attention: Jeffrey S. Bauer
 5051 New Centre Drive
 Suite 103
 Wilmington, NC 28403
4. LEGAL BASIS FOR SUBMISSION Lodine® Capsules, 300 mg
 (Wyeth Ayerst, NDA 18-922, patent expired 01/31/91;
 exclusivity for treatment of arthritis until 06/28/99.)
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME N/A
7. NONPROPRIETARY NAME Etodolac Capsules, 300 mg
8. SUPPLEMENT(s) PROVIDE(s) FOR N/A
9. AMENDMENTS AND OTHER DATES
10. PHARMACOLOGICAL CATEGORY NSAID
11. Rx or OTC Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM
 Capsules
14. POTENCY
 300 mg

15. CHEMICAL NAME AND STRUCTURE
 (±)-1,8-Diethyl-1,3,4,9-tetrahydro-
 pyrano[3,4-b]indole-1-acetic acid

$C_{17}H_{21}NO_3$ [41340-25-4]
 M.W. = 287.36



16. RECORDS AND REPORTS N/A
17. COMMENTS
18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: APPROVAL. (That is, if it weren't for
 unresolved dissolution issues, and labeling).
19. REVIEWER: J. L. Smith DATE COMPLETED: November 25, 1997

cc: ANDA 74-929
 DIV FILE
 Field Copy
 Reading File

Endorsements:

HFD-623/J.Smith/
 HFD-623/V.Sayeed/
 HFD-617/J.Wilson, PM/
 Y:\NEW\FIRMSAM\AESGEN\LTRS&REV\74929AP3.CD
 F/T by: gp/1/2/98

11/25/97
 11/24/97
 1/2/98