PRODUCT MONOGRAPH

ETODOLAC

Etodolac Capsules BP

200 mg and 300 mg

ANTI-INFLAMMATORY AGENT

AA PHARMA INC.
1165 Creditstone Road, Unit #1
Vaughan, Ontario
L4K 4N7

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PRODUCT MONOGRAPH

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THERAPEUTIC CLASSIFICATION

Anti-inflammatory Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Etodolac is a nonsteroidal anti–inflammatory drug (NSAID) that exhibits anti–inflammatory, analgesic and antipyretic properties in animal models. The pharmacological actions of etodolac are thought to be related to inhibition of prostaglandin biosynthesis at the site of inflammation.

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 and the R– form is not. Both enantiomers are stable and there is no R–to–S conversion *in vivo*.

According to *in vitro* studies of human chondrocytes, etodolac may preserve collagen phenotype while still inhibiting prostaglandin (PGE_2) biosynthesis. The results demonstrated that normal chondrocyte function remained unaffected by etodolac, as assessed by the rate of DNA synthesis, proteoglycan synthesis, type II collagen production, and collagenase production. Etodolac maintained type II collagen synthesis and partially blocked the effects of interleukin–1 (IL–1). Nevertheless, PGE_2 synthesis was significantly decreased in the presence of etodolac. These results need to be verified through *in vivo* testing.

Pharmacokinetics

Etodolac is well absorbed following oral administration. The systemic availability of etodolac is at least 80%, and the drug does not undergo significant first–pass metabolism. 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. Etodolac is more than 99% bound to plasma proteins.

Table of Etodolac Steady–State Pharmacokinetic Parameters (n=267)		
Kinetic Parameters	Scientific Notation (Units)	Mean ± SD
Extent Of Oral Absorption (Bioavailability)	F(%)	≥80
Peak Concentration Time	t_{max} (hr)	1.7 ± 1.3
Oral–Dose Clearance	CL/F (mL/hr/kg)	47 ±16
Central Compartment Volume	V_c/F (mL/kg)	132 ±47
Steady–State Volume	V_{ss}/F (mL/kg)	362 ±129
Distribution Half–Life	$t_{½}$ α (hr)	0.71 ± 0.50
Terminal Half–Life	$t_{½}$ β (hr)	7.3 ± 4.0

Mean 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. The mean plasma clearance of etodolac is 47 (±16) mL/hr/kg, and terminal disposition half–life is 7.3 (±4.0) hours.

Etodolac is extensively metabolized in the liver, with renal elimination of etodolac and its metabolites being the primary route of excretion. 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. Therefore, enterohepatic circulation, if present, is not extensive.

The extent of absorption of etodolac is not affected when it is administered after a meal or with an antacid. 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. Co–administration with an antacid decreases the peak concentration reached by about 15–20%, with no measurable effect on time–to–peak.

In studies in the elderly, age was found to have no effect on etodolac half-life or protein binding, and there was no drug accumulation. Etodolac clearance was reduced by about 15%. Because the reduction in clearance is small, 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, and they may be more sensitive to antiprostaglandin effects than younger patients.

In studies of the effects of mild to moderate renal impairment, no significant differences in the disposition of total and free etodolac were observed. 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. No adjustment of etodolac is generally required in patients with mild to moderate renal impairment; however, 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.

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.

Comparative Bioavailability

A standard, randomized, two–way crossover study was conducted in 24 healthy, adult, male volunteers to evaluate the relative bioavailability of single oral doses (300 mg) of ETODOLAC capsules and Ultradol® capsules. The mean pharmacokinetic parameters of the 23 subjects completing the study are listed below:

Summary Table of the Comparative Bioavailability Data Etodolac (Dose: 300 mg) From Measured Data			
Geometric Mean Arithmetic Mean (CV%)			
Parameter	ETODOLAC	Ultradol®⊥	Ratio of Means (%)
AUC_T	93.60	97.03	96.6
(mcg·hr/mL)	97.25 (30)	100.99 (31)	
AUC_I	96.45	100.18	96.5
(mcg·hr/mL)	100.88 (34)	105.20 (36)	
C_{max}	17.53	19.99	88.1
(mcg/mL)	17.80 (18)	20.76 (28)	
T_{max} (hr)*	1.60 (42)	1.71 (61)	-
$t_{½}$ (hr)*	7.03 (25)	7.12 (30)	-
* The T_{max} and $t_{½}$ parameters are expressed as the arithmetic means (CV%).			
⊥ Ultradol® is manufactured by Procter & Gamble Pharmaceuticals Canada Inc. and was purchased in Canada.			

INDICATIONS AND CLINICAL USE

ETODOLAC is indicated for acute or long–term use in the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis (degenerative joint disease).

CONTRAINDICATIONS

ETODOLAC should not be used in patients who have previously shown hypersensitivity to etodolac. Due to possible cross–reactivity, ETODOLAC should not be administered to patients who experience asthma, rhinitis, urticaria or other allergic reactions during therapy with ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals.

ETODOLAC should not be used in patients with an active peptic ulcer or inflammatory diseases of the gastrointestinal tract.

WARNINGS

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti–inflammatory drugs (NSAIDs) including etodolac.

ETODOLAC should be given under close medical supervision to patients prone to gastrointestinal tract irritation, particularly those with a history of peptic ulcer, melena, diverticulosis or other inflammatory disease of the gastrointestinal tract (such as ulcerative colitis or Crohn's disease). In these cases the physician must weigh the benefits of treatment against the possible hazards (see CONTRAINDICATIONS and ADVERSE EFFECTS).

Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur at any time during treatment, without warning symptoms or signs.

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from NSAIDs. As with other NSAIDs, ETODOLAC should be used with special caution and under close supervision in these patients and consideration should be given to a starting dose lower than usual, with individual adjustment when necessary.

Pregnancy and Lactation

The safety of ETODOLAC during pregnancy and lactation has not been established and therefore its use during pregnancy and lactation is not recommended.

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 metatarsal in rabbits. These were observed at dose levels (2–14 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.

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 labour and delivery in pregnant women are unknown.

It is not known whether etodolac is excreted in human milk. Caution should be exercised if ETODOLAC is administered to a nursing woman because many drugs are excreted in human milk.

Children

The safety and effectiveness of ETODOLAC in children have not been established and therefore, the drug is not recommended in this age group.

PRECAUTIONS

Gastrointestinal

If peptic ulceration is suspected or confirmed or if gastrointestinal bleeding or perforation occurs in patients under treatment with ETODOLAC, the drug should be immediately withdrawn, an appropriate treatment initiated and the patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H_2–receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of ETODOLAC therapy when and if the adverse reactions appear.

Renal Function

As with other NSAIDs, long–term administration of etodolac 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.

In patients with prerenal conditions leading to reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion, administration of nonsteroidal anti–inflammatory agents may precipitate overt renal decompensation due to a dose–dependent reduction in prostaglandin formation. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly.

Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Etodolac and its metabolites are eliminated primarily by the kidneys; therefore, the drug should be used with great caution in patients with impaired renal function. In these cases, lower doses of ETODOLAC should be considered and patients carefully monitored. During long–term therapy, kidney function should be monitored periodically.

Hepatic Function

As with other NSAIDs, 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. Meaningful (3 times the upper limit of normal) elevations of ALT (SGPT) or AST (SGOT) occurred in controlled clinical trials with etodolac in approximately 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug 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.), this drug should be discontinued.

During long–term therapy, liver function tests should be monitored periodically. If this drug is to be used in the presence of impaired liver function, it must be done under strict observation.

Fluid and Electrolyte Balance

Fluid retention and edema have been reported; therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. ETODOLAC should be used with caution in patients with heart failure, hypertension and renal diseases and in those recovering from surgical operations under general anesthesia and other conditions predisposing to fluid retention. With NSAID treatment, there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure, elderly patients or in patients receiving concomitant

therapy with beta–adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics.

Serum electrolytes should be monitored periodically during long–term therapy, especially in those patients at risk.

Hematology

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function and vascular response to bleeding to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when ETODOLAC is administered.

Blood dyscrasias associated with the use of NSAIDs are rare, but could be with severe consequences.

Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by NSAIDs, which may produce fluid retention or minor gastrointestinal blood loss in some patients. Therefore, patients with initial hemoglobin values of 10 g/dL or less who are to receive long–term therapy, should have hemoglobin values determined frequently.

Infection

In common with other anti–inflammatory drugs, etodolac may mask the usual signs of infection.

Ophthalmology

Blurred and/or diminished vision has been reported with the use of etodolac and other NSAIDs. If such symptoms develop, this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Hypersensitivity

As with other nonsteroidal anti–inflammatory drugs, allergic reactions, including anaphylactic/ anaphylactoid reactions, can occur without prior exposure to drug; therefore, careful questioning of patients for a history of asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs before starting therapy is important.

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 15–20% but have no detectable effect on the time–to–peak.

Acetylsalicylic acid (ASA): When etodolac is administered with ASA, 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 ASA is not generally recommended because of potential of increased adverse effects.

Warfarin: Concomitant administration of warfarin and etodolac results in reduced protein binding of warfarin, but there is no change in the clearance of free warfarin. There is 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. Caution should be exercised, nevertheless, because interactions have been seen with other NSAIDS.

Phenytoin: Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin.

Glyburide: Etodolac has no apparent pharmacokinetic or pharmacodynamic interaction when administered with glyburide.

Diuretics: Etodolac has no apparent pharmacokinetic interaction when administered with furosemide or hydrochlorothiazide, nor does etodolac attenuate the diuretic response of either of these drugs in normal volunteers. ETODOLAC, and other NSAIDs nevertheless, should be used with caution in patients receiving diuretics or who have cardiac, renal or hepatic failure (see Renal Function).

Antihypertensive Agents: NSAIDs can reduce the anti-hypertensive effect of propranolol and other beta-blockers as well as other antihypertensive agents.

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 (monitoring of plasma drug levels).

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 ibuprofen, acetaminophen, phenytoin, probenecid, indomethacin, chlorpropamide, glyburide, naproxen, glipizide or piroxicam.

In contrast, phenylbutazone causes an 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 co–administration of phenylbutazone, it is not recommended that they be co–administered.

Laboratory Test Interactions

The urine of patients who take etodolac can give a false–positive reaction for urinary bilirubin (urorubin) 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 1-2 mg% 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 one year of therapy.

ADVERSE REACTIONS

The most common adverse reactions encountered with nonsteroidal anti–inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion, particularly in the elderly.

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 post–marketing surveillance studies in approximately 60,000 patients.

In clinical studies, etodolac was generally well tolerated. Most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials because of adverse events, was 9% for patients treated with etodolac.

Listed below are the patient complaints with an incidence of greater than, equal to, or less than 1% which occurred in clinical trials and post–marketing experience with etodolac at doses up to 1000 mg per day.

Incidence ≥1%

Gastrointestinal: nausea; diarrhea; epigastric pain; heartburn; indigestion; flatulence; abdominal pain; gastrointestinal cramps; abdominal distention; constipation; vomiting; dyspepsia; gastritis; melena.

Central Nervous System: headache; dizziness; drowsiness; insomnia; nervousness/anxiety; depression.

Dermatologic: dermatitis manifested as skin rash (erythematous, vesicular, maculopapular, morbilliform, petechial, or eczematous), or pruritus.

General Illness: fatigue; weakness/malaise.

Genitourinary: urinary frequency; dysuria.

Metabolic System: fluid retention/edema.

Eye, Ear, Nose and Throat: tinnitus; blurred vision.

Incidence <1%

Gastrointestinal: peptic ulcer with/without gastrointestinal hemorrhage and/or perforation; hematemesis; rectal bleeding; stool changes (loose, with mucus, or increase in number and/or frequency); taste abnormalities including loss of taste; eructation; stomatitis; hepatitis; cholestasis; jaundice; esophagitis with or without erosions or stricture or cardiospasm; colitis; pancreatitis.

Central Nervous System: restlessness; confusion; vertigo; syncope; nightmares; listlessness; inability to concentrate, somnolence.

Dermatologic: urticaria; angioedema; alopecia; sore, dry, inflamed or swollen mucous membranes including mouth, tongue, and lips; photosensitivity; peeling; easy bruising; brittle nails; exfoliative dermatitis; Stevens–Johnson syndrome, cutaneous vasculitis with purpura; erythema multiforme.

Eye, Ear, Nose and Throat: hearing loss, visual disturbances including teichopsia; epistaxis; ear ache; pressure/throbbing in ears; burning sensation of eyes/nose; twinging behind eyes; photophobia; conjunctivitis.

Extremities: paresthesias; muscle cramps; muscular fatigue; involuntary muscle movement; pain in arms/hands/shoulders; hand tremor; tenderness; subcutaneous nodule/first metatarsophalangeal joint.

General Illness: pyrexia; chills; lethargy; vasculitis; general deterioration; breast tenderness.

Genitourinary: dysuria; urinary urgency; hematuria; nocturia; vaginal bleeding; difficulty maintaining erection; recto–pubic pain; cystitis; leukorrhea; renal calculus; interstitial nephritis; papillary necrosis; renal failure; uterine bleeding irregularities.

Metabolic System: change in weight; change in appetite; flushing; anorexia; excessive thirst; hot flashes; diaphoresis.

Cardiovascular: hypertension; congestive heart failure; palpitations; tachycardia; chest pain (costal, costochondral, or retrosternal); arrhythmias; myocardial infarction; and chest tightness or fullness.

Respiratory: dyspnea; asthma; bronchospasm; hyperventilation; sneezing and sighing; bronchitis; pharyngitis; rhinitis; sinusitis.

Hypersensitivity: anaphylactic/anaphylactoid reaction; laryngeal edema.

Hematology: agranulocytosis; pancytopenia; decreased hemoglobin; decreased hematocrit; anemia; hemolytic anemia; thrombocytopenia; leukopenia; neutropenia; eosinophilia; atypical lymphocytes; increased bleeding time.

Laboratory: elevated hepatic enzymes; increased serum creatinine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

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.

Treatment

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 with symptoms or following a large overdose (5-10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, alkalinization of the urine, hemodialysis or hemoperfusion would probably not be useful due to etodolac's high protein binding.

One case of intentional etodolac overdosage has been reported (Human Toxicol 1988; 7: 203-204). This 53–year–old female ingested from 15 to 46 two hundred mg etodolac capsules (3 to

8.6 grams). Plasma etodolac concentrations were measured frequently over the next 4 days. At 5 hours after ingestion (3 hours after gastric lavage) the plasma etodolac level was 22 μg/mL. These plasma levels and her subsequent recovery with no signs or symptoms of etodolac toxicity were consistent with systemic absorption of 600 to 800 mg. Her laboratory tests on admission showed a prolonged prothrombin time and a false–positive urine bilirubin (attributed to the phenolic etodolac metabolites).

DOSAGE AND ADMINISTRATION

Adults

The recommended dosage of ETODOLAC in the treatment of rheumatoid arthritis and osteoarthritis is 200 to 300 mg twice daily. Patients may also respond to a single daily (400 mg or 600 mg) dose administered in the evening.

The safety of doses in excess of 1000 mg per day for extended periods has not been established. In order to maximize the effectiveness of therapy, the dosage must be individualized for each patient.

Elderly

As with any NSAID, 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 otherwise healthy patients 65 years and older, no substantial differences in the side-effects profile of etodolac were seen.

PHARMACEUTICAL INFORMATION

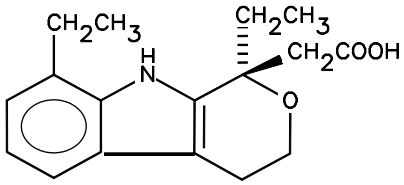
Drug Substance

Proper/Common Name: Etodolac

Chemical Names: 1) Pyrano[3,4-*b*]indole–1–acetic acid,1,8–diethyl–1,3,4,9–tetrahydro–;

2) 1,8–Diethyl–1,3,4,9–tetra–hydropyrano[3,4-*b*]indole–1–acetic acid.

Structural Formula:



and enantiomer

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

Molecular Weight: 287.4

Description: Etodolac is a white to almost white crystalline powder. Practically insoluble in water, freely soluble in ethanol (96%).

Composition

ETODOLAC contains the following non–medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, stearic acid and talc. The capsule contains black iron oxide, edible ink, gelatin, sodium lauryl sulfate – as a processing aid, titanium dioxide and

yellow iron oxide. The ink contains erythrosine aluminum lake, iron oxide yellow, n-butyl alcohol, propylene glycol, shellac and titanium dioxide.

Stability and Storage Recommendations

Store at room temperature (15-30°C) and protect from moisture.

AVAILABILITY OF DOSAGE FORMS

ETODOLAC 200 mg Capsules: Each hard gelatin, light grey/dark grey, size #1 capsule imprinted "200" contains 200 mg etodolac. Available in bottles of 60, 100, 250, 500 and 1000, unit dose packages of 30 and 100 capsules.

ETODOLAC 300 mg Capsules: Each hard gelatin, light grey/light grey, size #0 capsule imprinted "300" contains 300 mg etodolac. Available in bottles of 60, 100, 250 and 500, unit dose packages of 30 and 100 capsules.

INFORMATION FOR THE CONSUMER

ETODOLAC, which has been prescribed to you by your physician, is one of a large group of nonsteroidal anti–inflammatory drugs (NSAIDs) and is used to treat the symptoms of certain types of arthritis. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and helping to control inflammation and other body reactions.

You should take ETODOLAC only as directed by your physician. Do not take more of it, do not take it more often and do not take it for a longer period of time than your physician ordered.

Be sure to take ETODOLAC regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. During treatment, your physician may decide to adjust the dosage according to your response to the medication.

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your physician.

Do not take ASA (acetylsalicylic acid), ASA–containing compounds or other drugs used to relieve symptoms of arthritis while taking ETODOLAC unless directed to do so by your physician.

If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medication is not causing unwanted effects.

Along with its beneficial effects, ETODOLAC like other NSAIDs, may cause some undesirable reactions. Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur they may require medical attention. Check with your physician immediately if any of the following are noted:

– bloody or black tarry stools;

– shortness of breath, wheezing, any trouble in breathing or tightness in the chest;

– skin rash, swelling, hives or itching;

– indigestion, nausea, vomiting, stomach pain or diarrhea;

– yellow discolouration of the skin or eyes, with or without fatigue;

– any changes in the amount or colour of your urine (such as dark; red or brown);

– swelling of the feet or lower legs;

– blurred vision or any visual disturbance;

– mental confusion, depression, dizziness, lightheadedness; hearing problems.

ALWAYS REMEMBER

Before taking this medication tell your physician and pharmacist if you:

– are allergic to etodolac or other related medicines of the NSAID group such as acetylsalicylic acid, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid, or tolmetin;

– have a history of stomach upset, ulcers, or liver or kidney diseases;

– are pregnant or intend to become pregnant while taking this medication;

– are breast feeding;

– are taking any other medication (either prescription or non–prescription);

– have any other medical problem(s).

<u>While taking this medication</u>:

– tell any other physician, dentist or pharmacist that you consult or see, that you are taking this medication;

– be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication;

– check with your doctor if you are not getting any relief or if any problems develop.

– report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.

– your regular medical checkups are essential.

– If you require more information on this drug, consult your physician or pharmacist.

ETODOLAC is not recommended for use in children.

PHARMACOLOGY

Etodolac showed dose–related anti–inflammatory properties in rats with established Freund's adjuvant–induced arthritis. An oral dose of 0.5 mg/kg produced a therapeutic effect (decrease 0.5 mL hindleg volume from day 14) in one–third of treated rats whereas 5 mg/kg produced a therapeutic effect in all treated rats. The ED_{50} was 0.7± 0.13 mg/kg. Etodolac reduced the incidence and severity of the bone and articular lesions associated with adjuvant arthritis and reversed the progress of the condition. It was also effective in reducing acute inflammation and preventing the secondary response in the non–injected hindpaw in the same model.

In the carrageenin paw edema test, etodolac was as potent as phenylbutazone; an oral dose of 36 mg/kg produced a 50% inhibition of the induced foot edema.

Etodolac was administered p.o. daily for 28, 56, or 84 days at a dose of 8 mg/kg to rats with established arthritis induced by the injection of Freund's complete adjuvant into the tail. Rats which, at the beginning of treatment, had lost the use of their hindlimbs progressively recovered this function, and after 84 days hindleg function was 94% of normal. Other symptoms of the disease (hindpaw edema and depressed body weight gain) were also reduced. Furthermore, radiological and histological analyses of the hindlimbs of treated and untreated animals showed that etodolac greatly diminished the bone demineralization, periosteal reaction, soft tissue swelling and joint space narrowing which were characteristic of the disease. When treatment with etodolac was stopped after 56 days, there was little or no signs of recurrence of the disease over the next 28 days.

At equivalent doses, naproxen and ibuprofen halted, but, unlike etodolac, did not reverse the progress of the disease. Furthermore, the beneficial effects on edema, hindleg function and body weight appeared much later with naproxen and ibuprofen than with etodolac. ASA at 300 mg/kg per day had little effect.

Like other nonsteroidal anti–inflammatory drugs, etodolac was only weakly effective on local application. It did not affect the passive Arthus reaction in rats nor the delayed hypersensitivity reaction in mice. The increase in capillary permeability evoked by passive cutaneous anaphylaxis or by the intradermal injection of either histamine or serotonin in rats was not antagonized by orally administered etodolac.

In vitro, etodolac inhibited either the synthesis and/or release of the slow reacting substance of anaphylaxis from sensitized guinea pig lung tissue.

Etodolac caused dose–related analgesia in the Randall-Sellito test in rats following oral administration (ED_{50} = 4.7 mg/kg). It was weakly effective in the phenylquinone–induced writhing test in mice (ED_{50} = 154 mg/kg p.o.) and this effect was not antagonized by naloxone. Like other anti–inflammatory drugs, it was not effective in the tail flick test in mice. At concentrations corresponding to serum levels of 5 to 43 μg/mL, etodolac had negligible binding affinity for rat brain opiate receptors.

Oral doses of 5 to 20 mg/kg of etodolac showed antipyretic activity in rats rendered hyperthermic by the subcutaneous injection of a yeast suspension. Etodolac had no effect on rectal temperature in normal rats.

In starved rats given single oral doses, etodolac was less irritating to the gastric mucosa than naproxen, indomethacin, sulindac, ibuprofen, and tolmetin, and slightly more irritating than phenylbutazone. In fed rats, it was more irritating to the intestinal than to the gastric mucosa. It did not affect spontaneous gastric acid secretion in rats or intestinal motility and tonus in cats. Etodolac had no effect on glomerular filtration rate, renal blood flow, urine volume or electrolyte excretion in rats. It decreased furosemide–induced diuresis.

Etodolac inhibited the biosynthesis of prostaglandins *in vitro*. It also demonstrated a low degree of PGE_2 synthesis inhibition in rat gastric mucosa. It inhibited collagen–induced platelet aggregation in rat blood and slightly inhibited it in human blood *in vitro*, but it did not affect adenosine diphosphate–induced platelet aggregation in either rat or human blood. The second phase of epinephrine–induced platelet aggregation in human blood was inhibited *in vitro*.

Etodolac did not affect bronchoconstriction in anesthetized rats or guinea pigs or respiratory movement in anesthetized cats. It did not inhibit monoamine uptake and showed no effects on the central nervous system in a variety of tests. Etodolac had no effects *in vitro* on the guinea pig right or left atrium, nor did it cause any significant cardiovascular effects in rats, cats or dogs.

Clinical Experience

Etodolac has been studied in double–blind, randomized, parallel–group, multicentre clinical trials in the treatment of rheumatoid arthritis and osteoarthritis. In rheumatoid arthritis studies, etodolac 200 mg twice a day was compared with naproxen 500 mg twice a day, piroxicam 20 mg once a day, or diclofenac 50 mg three times a day. In osteoarthritis studies, etodolac 200 mg three times a day was compared with diclofenac 50 mg three times a day, and etodolac 300 mg twice a day was compared with piroxicam 20 mg once a day, or naproxen 500 mg twice a day.

Results of these rheumatoid arthritis and osteoarthritis studies showed etodolac to be comparable to naproxen, piroxicam and diclofenac. Key efficacy parameters improved significantly ($p<0.05$) in all treatment groups with no significant differences between therapies.

Special Studies

Etodolac was compared to other NSAIDs in studies focusing on gastrointestinal (GI) microbleeding, endoscopy, and gastroduodenal prostaglandin assays. The clinical significance of these results is unknown.

In gastrointestinal microbleeding studies of healthy individuals, the GI blood loss observed with etodolac (600 mg to 1200 mg per day) was similar to that seen with placebo and significantly less than that seen with acetylsalicylic acid (ASA) (2600 mg per day), ibuprofen (2400 mg per day), indomethacin (200 mg per day), or naproxen (750 mg per day). In a study of etodolac (600 mg and 1000 mg per day) and piroxicam (20 mg per day), GI blood loss observed with etodolac was comparable with that seen with placebo and significantly less than that seen with piroxicam.

With endoscopy studies in healthy volunteers, etodolac treatment (up to 1200 mg per day) resulted in endoscopy scores which were similar to baseline and placebo, and significantly better than following treatment with ASA (3900 mg per day), ibuprofen (2400 mg per day), indomethacin (200 mg per day), or naproxen (1000 mg per day). The effects of etodolac (600 mg to 1200 mg per day) and diclofenac (150 mg per day) were not significantly different from each other or from baseline, as shown by endoscopy. GI microbleeding and endoscopy studies provide an objective measure of blood loss and lesions.

Prostaglandin assays of the gastroduodenal mucosa of patients with active rheumatoid arthritis were performed in a double-blind randomized study involving therapeutic doses of etodolac (600

mg per day) and naproxen (1000 mg per day). Biopsies were taken at baseline and after 4 weeks of treatment. The results of this study indicate that etodolac does not appear to affect gastric or duodenal prostaglandin synthesis.

TOXICOLOGY

Acute Toxicity

The oral and intraperitoneal (i.p.) LD_{50} was determined in mice, rats and guinea pigs, and rabbits (preliminary supportive study). The results are shown in the following tables.

LD_{50} (mg/kg) of Etodolac in Mice, Rats and Guinea Pigs		
Species and Route of Administration	LD_{50} mg/kg (95% Confidence Limits)	
	Males	Females
Mouse		
-p.o.	883 (628-1288)	1141 (954-1566)
-i.p.	333 (266-367)	379 (346-409)
Rats		
-p.o.	78 (70-88)	191 (148-257)
-i.p.	116 (99-134)	151 (125-199)
Guinea pig		
-p.o.	1000 (*)	1012 (898-1118)
-i.p.	437 (392-479)	412 (350-449)
*Mortality appeared to plateau at doses between 950 and 1225 mg/kg and therefore the 95% confidence limits could not be calculated.		

Mouse: Drug–related effects occurring in mice after both oral and i.p. administration were tremors, ataxia, dyspnea, hypoactivity, clonic convulsions, and ptosis. Bradypnea and salivation were seen only after oral administration.

Rat: Drug–related effects observed in rats after both oral and i.p. administration included ataxia, hypoactivity, ptosis, yellow fluid around the genitalia, and poor physical condition. In addition, red

pigmentation was seen around the mouth or nose after oral administration, and low carriage was seen after i.p. administration.

Guinea Pig: Etodolac was administered orally and intraperitoneally to guinea pigs. Drug effects observed after oral administration included, hypoactivity, ptosis, tremors, and emaciation (males only). Drug effects observed after i.p. dosing included paddling, bradypnea, dyspnea, immobility, and yellow discolouration around the genitals or on the pelage, hypoactivity, ptosis, tremors, clonic convulsions, salivation, ataxia, and hyperactivity.

The LD_{50} was determined orally and i.p. in additional preliminary supportive studies in mice and rats. The results are shown in the table below.

LD_{50} (mg/kg) of Etodolac in Mice and Rats		
Species and Route of Administration	Males LD_{50} (mean range)	Females LD_{50} (mean range)
Mouse		
Oral	822 (558-1208)	1188 (826-1704)
I.P.	387 (257-587)	419 (275-640)
Rat		
Oral	72 (50-103)	113 (90-142)
I.P.	104 (81-132)	133 (112-158)

In both species, the main toxic effects observed after oral and i.p. administration were ataxia, reduced motor activity, dyspnea, ptosis, and clonic convulsions.

The LD_{50} was determined orally and i.p. in additional preliminary supportive studies in rabbits. The results are shown in the table below:

LD_{50} (mg/kg)of Etodolac in Rabbits		
Route of Administration	Dosages (mg/kg)	LD_{50} (±95% Confidence Limits)
Oral	2000-2500	2250 (2064-2452)
I.P.	341-500	390 (350-435)

Rabbit: Drug effects observed after both routes of administration were sedation, hypomotility, ataxia, and loss of postural reflex.

Subacute And Chronic Toxicity

Etodolac was administered orally to mice for 18 months at dosages ranging from 0-15 mg/kg; orally to rats for three weeks, two and six months, and two years with dosages ranging from 0-45 mg/kg; and orally to dogs for six months and one year with dosages ranging from 0-90 mg/kg.

Mouse: An oral range finding study conducted in the mouse for 21 days showed no drug effect at dosages of 3, 9, 15, or 20 mg/kg. However, in light of drug effects occurring in the first six months of a two year rat study at 9 and 15 mg/kg, it appeared appropriate to limit the dosages for an 18 month mouse study to 3, 9, and 15 mg/kg. This dosage selection was further supported by preliminary drug metabolism data suggesting that rats and mice had similarities in t_{max} values and elimination half-lives.

Eighteen–Month Oral Toxicity Study

After eighteen months of drug administration to mice at dosages ranging from 3 to 15 mg/kg, etodolac was not considered tumorigenic. No drug–related changes occurred in physical appearance, behaviour, body weight, food consumption, clinical chemistry, or ophthalmologic

findings. The lymphocyte to neutrophil ratio was reversed in the 15 mg/kg males, but no other changes occurred in hematologic values.

Males and females in the 15 mg/kg etodolac–treated group had decreased survival. These deaths could not be directly related to the administration of etodolac. No etodolac effects were observed in the 3 and 9 mg/kg groups.

Rats

Three–Week Toxicity Study

Etodolac was administered to rats for three weeks to compare the toxicity via gavage versus diet routes of drug administration. Dosage–related mortality from intestinal lesions occurred with 12, 16, 20 mg/kg in the males and 20 mg/kg in the females, and the incidence was significantly greater in the rats treated via gavage. An associated decrease in body weight gain, or weight loss, generally with concomitant alterations in food consumption occurred. Drug–related physical examination findings, hematologic, and clinical chemistry alterations were considered secondary effects due to a direct effect of etodolac on the intestinal tract and resulting ulceration and inflammation.

A similar spectrum of toxicologic changes, including pathologic lesions in the intestinal tract, has been observed in previous long–term studies.

Two-Month Toxicity Study (Preliminary Supportive Study)

Etodolac was orally administered at dosages ranging from 2 to 45 mg/kg. Rats receiving 45 mg/kg/day died within the first ten days of the study. Examination of the gastrointestinal tract

of these animals revealed gastric ulcerations. A significant increase in the coagulation time for both sexes occurred in the 6 mg/kg group. Postmortem examination did not reveal any pathological lesions that were considered to be related to these dosages of etodolac.

Six–Month Toxicity Study

Etodolac was administered orally to rats at dosages ranging from 2 to 10 mg/kg. An increase in the mean relative kidney–to–body weight ratio of the males occurred in the 10 mg/kg group, which was significantly greater than that of the controls. The concentrations of etodolac in the serum were dosage–related and tended to be higher in the female rats than in the males.

Two–Year Oral Toxicity Study

Etodolac was considered to be non–tumorigenic after oral administration to rats at dosages ranging from 3 to 15 mg/kg for two years. Adverse effects on survival, general behaviour, and appearance and secondary alterations in hematologic values occurred in the 15 mg/kg group and to a lesser extent in some rats receiving 9 mg/kg. Variations in body weight occurred in the etodolac–treated rats throughout the study; however, at the end of the study, the values were generally comparable to the control values. Etodolac–induced, dosage–related histopathologic lesions of the gastrointestinal tract (ulceration) and kidney (papillary necrosis) occurred in rats receiving 9 and 15 mg/kg, with a few rats at the 3 mg/kg dosage also affected.

Dogs

Six–Month Toxicity Study

Etodolac was orally administered to dogs at dosages ranging from 15 to 90 mg/kg. One female in the 90 mg/kg group died with an intestinal intussusception; however, a clear relationship to drug administration could not be established. Gross examination of the intestinal tract showed erosions in animals in all drug–treated groups. Microscopic examination confirmed erosion of the intestinal mucosa in the 15 and 90 mg/kg dosage groups. Evidence of ulceration of the colon was seen in the 90 mg/kg group. Mean body weights of the females in the 90 mg/kg group were generally 10% lower, and food consumption was somewhat less than that in the control group throughout the study.

Readily detectable serum etodolac concentrations were found in all but one of the treated dogs; however, the degree of variability precluded an assessment of dosage–dependence.

One–Year Oral Toxicity Study

Etodolac was administered orally at dosages ranging from 10 to 80 mg/kg. Three males and three females of the eight dogs in the 80 mg/kg group were found dead or were killed in *extremis* during the study. The administration of etodolac induced intestinal ulceration, mainly in the jejunum and ileum and frequently associated with Peyer's patches, in two males and one female of the 40 mg/kg group and in four males and three females of the 80 mg/kg group. One high–dosage female dog also had drug–related tubular nephrosis. The deaths of three males and three females of the 80 mg/kg group during the course of the study resulted from intestinal ulceration and the sequelae of anemia, emaciation, and peritonitis.

Etodolac was well tolerated at a dosage of 10 mg/kg per day for 52 weeks. Body weight loss associated with decreased food consumption, emesis, and fecal alterations were observed in all the dogs that died, and to a lesser extent, in the surviving male dog in the 80 mg/kg group. Physical examination findings, hematologic, clinical chemistry, and urinalysis alterations were considered secondary effects.

Mutagenicity

Etodolac was non–mutagenic in the Salmonella mutagenesis assay (Ames Test), thymidine kinase forward mutation assay using mouse lymphoma cell line L5178Y, *in vivo* micronucleus test using CD–1 mice, and in additional ancillary preliminary supportive studies which included Salmonella mutagenesis assay (Ames Test), *Saccharomyces cerevisiae* D4 gene conversion test, *Schizosaccharomyces pombe* P1 gene mutation assay, unscheduled DNA synthesis assay, reverse mutation assay of urinary etodolac metabolites using *Saccharomyces cerevisiae* D4, and a host mediated assay measuring reverse mutation frequency of *Saccharomyces cerevisiae* D4.

Reproduction And Teratology

Fertility Studies in Rats

Oral dosages ranging from 3 to 16 mg/kg of etodolac were used in the Segment I studies. Male and female rat mating performance and pregnancy (i.e., conception) rates were not affected by etodolac treatment at the highest dosage (16 mg/kg). Female treatment resulted in increased pre–implantation loss at dosages of 8 to 16 mg/kg and increased post–implantation loss at dosages of 15 and 16 mg/kg. In fertility studies in which females were allowed to deliver, gestational lengths were increased at dosages of 3 mg/kg and above, and prolonged deliveries, dystocia, and an inability to complete parturition occurred reproducibly at dosages of 9 mg/kg and

above; maternal death sometimes accompanied the dystocia. Postnatal pup survival was also reproducibly decreased at dosages of 9 mg/kg and above. The reproductive effects occurred at dosages that also produced maternal gastrointestinal or renal lesions and associated changes in appearance. The effects on parturition and offspring survival in rats are characteristic for drugs that inhibit prostaglandin synthesis.

Teratology Studies

Mouse: A mouse Segment II study conducted at oral dosages ranging from 2 to 10 mg/kg did not reveal an effect of maternal etodolac treatment on offspring *in utero* survival, growth, or morphological development at the highest dosage (10 mg/kg).

Rats: Rat Segment II studies were conducted at oral dosages ranging from 2 to 22 mg/kg. There were no effects of maternal drug treatment on offspring *in utero* survival, growth, or morphological development at the highest dosage (22 mg/kg), although maternal toxicity (e.g. postmortem findings, effects on survival, appearance, body weight gain, and food consumption) was evident at dosages of 6 mg/kg and above. In a Segment II study in which some of the dams from each group were allowed to deliver, there were no effects of maternal gestational drug treatment on offspring postnatal survival, growth, morphological, reflex, or behavioural development or on offspring reproductive performance.

Rabbit: Rabbit Segment II studies were conducted at oral dosages ranging from 2 to 128 mg/kg. There were no effects of maternal drug treatment on offspring *in utero* survival, growth, or morphological development. Maternal mortality, gastrointestinal erosions or ulcers and reduction in body weight gain and food consumption occurred at 128 mg/kg.

Perinatal/Postnatal Studies in Rats

Segment III studies were conducted at oral dosages ranging from 2 to 15 mg/kg. Gestational lengths were increased at dosages of 2 mg/kg and above. Prolonged deliveries, dystocia, inability to complete parturition, and occasional maternal deaths during parturition occurred at dosages of 4 mg/kg and above. Offspring postnatal survival was decreased at dosages of 4 mg/kg and above, accompanied by poor maternal litter care. There were no adverse effects of maternal drug treatment on offspring growth, morphological, reflex, or behavioural development or on offspring reproductive performance. The effects on parturition and offspring survival occurred at dosages that also produced gastrointestinal lesions and were characteristic of drugs such as etodolac, that inhibit prostaglandin synthesis.

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