ETODOLAC TABLETS USP

Bayshore Pharmaceuticals LLC.

Rx only

Cardiovascular Thrombotic Events

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [see **WARNINGS** and **PRECAUTIONS**].
- Etodolac tablets, 400 mg and 500 mg are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see **CONTRAINDICATIONS** and **WARNINGS**].

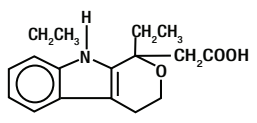
Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal (GI) events. (See **WARNINGS**.)

DESCRIPTION

Etodolac tablets, USP are members of the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each tablet contains etodolac for oral administration. Etodolac is a racemic mixture of [+]S and [-]R-enantiomers. Etodolac USP is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

The chemical name is (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. 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. The molecular formula for etodolac is $C_{17}H_{21}NO_3$, and it has the following structural formula:



Each tablet, for oral administration, contains 400 mg or 500 mg of etodolac USP. In addition, each tablet contains the following inactive ingredients: hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate and titanium dioxide. Also, each 400 mg tablet contains iron oxide red and iron oxide yellow. Each 500 mg tablet contains D&C Yellow #10 Aluminum Lake, FD&C Blue #1 Aluminum Lake and FD&C Red #40 Aluminum Lake.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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 completely understood, but may be related to prostaglandin synthetase inhibition.

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*.

Pharmacokinetics

Absorption

The systemic bioavailability of etodolac from etodolac capsules and tablets is 100% as compared to solution and at least 80% as determined from mass balance studies. 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 (C_{max}) range from approximately 14 ± 4 to 37 ± 9 µg/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 the area under the plasma concentration-time curve (AUC) 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. The extent of absorption of etodolac is not affected when etodolac tablets are 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.

Table 1. Mean (CV%)† Pharmacokinetic Parameters of Etodolac in Normal Healthy Adults and Various Special Populations

PK Parameters	Normal Healthy Adults (18-65)* (n=179)	Healthy Males (18-65) (n=176)	Healthy Females (27-65) (n=3)	Elderly (>65) (70-84)	Hemodialysis (24-65) (n=9) Dialysis	Hemodialysis (24-65) (n=9) Dialysis On Off	Renal Impairment (46-73) (n=10)	Hepatic Impairment (34-60) (n=9)
Tmax, h	1.4 (61%)†	1.4 (60%)	1.7 (60%)	1.2 (43%)	1.7 (88%)	0.9 (67%)	2.1 (46%)	1.1 (15%)
Oral Clearance, mL/h/kg (CL/F)	49.1 (33%)	49.4 (33%)	35.7 (28%)	45.7 (27%)	NA	NA	58.3 (19%)	42.0 (43%)
Apparent Volume of Distribution, mL/kg (Vd/F)	393 (29%)	394 (29%)	300 (8%)	414 (38%)	NA	NA	NA	NA
Terminal Half-Life, h	6.4 (22%)	6.4 (22%)	7.9 (35%)	6.5 (24%)	5.1 (22%)	7.5 (34%)	5.7 NA	5.7 (24%)

† %Coefficient of variation

* Age Range (years)

NA = not available

Distribution

The mean apparent volume of distribution (Vd/F) of etodolac is approximately 390 mL/kg. Etodolac is more than 99% bound to plasma proteins, primarily to albumin. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied. It is not known whether etodolac is excreted in human milk; however, based on its physical-chemical properties, excretion into breast milk is expected. 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.

Metabolism

Etodolac is extensively metabolized in the liver. The role, if any, of a specific cytochrome P450 system in the metabolism of etodolac is unknown. Several etodolac metabolites have been identified in human plasma and urine. Other metabolites remain to be identified. The metabolites include 6-, 7-, and 8-hydroxylated-etodolac and etodolac glucuronide. After a single dose of 14C-etodolac, hydroxylated metabolites accounted for less than 10% of total drug in serum. On chronic dosing, hydroxylated-etodolac metabolite does not accumulate in the plasma of patients with normal renal function. The extent of accumulation of hydroxylated-etodolac metabolites in patients with renal dysfunction has not been studied. The hydroxylated-etodolac metabolites undergo further glucuronidation followed by renal excretion and partial elimination in the feces.

Excretion

The mean oral clearance of etodolac following oral dosing is 49 (± 16) mL/h/kg. Approximately 1% of an etodolac dose is excreted unchanged in the urine with 72% of the dose excreted into urine as parent drug plus metabolite:

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

Although renal elimination is a significant pathway of excretion for etodolac metabolites, no dosing adjustment in patients with mild to moderate renal dysfunction is generally necessary. The terminal half-life ($t_{1/2}$) of etodolac is 6.4 hours (22% CV). In patients with severe renal dysfunction or undergoing hemodialysis, dosing adjustment is not generally necessary.

Fecal excretion accounted for 16% of the dose.

Special Populations

Geriatric

In etodolac clinical studies, no overall differences in safety or effectiveness were observed between these patients and younger patients. In pharmacokinetic 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. Therefore, no dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics (see **PRECAUTIONS, Geriatric Use**).

Etodolac is eliminated primarily by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **WARNINGS**, ***Renal Effects***).

Pediatric

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Race

Pharmacokinetic differences due to race have not been identified. Clinical studies included patients of many races, all of whom responded in a similar fashion.

Hepatic Insufficiency

Etodolac is predominantly metabolized by the liver. In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Patients with acute and chronic hepatic diseases do not generally require reduced doses of etodolac compared to patients with normal hepatic function. However, etodolac clearance is dependent on liver function and could be reduced in patients with severe hepatic failure. Etodolac plasma protein binding did not change in patients with compensated hepatic cirrhosis given etodolac.

Renal Insufficiency

Etodolac pharmacokinetics have been investigated in subjects with renal insufficiency. Etodolac renal clearance was unchanged in the presence of mild-to-moderate renal failure (creatinine clearance 37 to 88 mL/min). Furthermore, there were no significant differences in the disposition of total and free etodolac in these patients. However, etodolac should be used with caution in such patients because, as with other NSAIDs, it may further decrease renal function in some patients. 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. Etodolac is not significantly removed from the blood in patients undergoing hemodialysis.

CLINICAL TRIALS

Analgesia

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

Osteoarthritis

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

Rheumatoid Arthritis

In a 3-month study with 426 patients, etodolac 300 mg b.i.d. was effective in management of rheumatoid arthritis and comparable in efficacy to piroxicam 20 mg/day. In a long-term study with 1,446 patients in which 60% of patients completed 6 months of therapy and 20% completed 3 years of therapy, etodolac in a dose of 500 mg b.i.d. provided efficacy comparable to that obtained with ibuprofen 600 mg q.i.d. In clinical trials of rheumatoid arthritis patients, etodolac has been used in combination with gold, d-penicillamine, chloroquine, corticosteroids, and methotrexate.

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of etodolac tablets and other treatment options before deciding to use etodolac tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

Etodolac tablets are indicated:

- For acute and long-term use in the management of signs and symptoms of the following:
  1. Osteoarthritis
  2. Rheumatoid arthritis
- For the management of acute pain

CONTRAINDICATIONS

Etodolac tablets are contraindicated in patients with known hypersensitivity to etodolac or other ingredients in etodolac.

Etodolac tablets should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS, Anaphylactoid Reactions** and **PRECAUTIONS, Pre-existing Asthma**).

- In the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

WARNINGS

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as etodolac, increases the risk of serious gastrointestinal (GI) events [see **WARNINGS**].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see **CONTRAINDICATIONS**].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of etodolac tablets in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If etodolac tablets are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Hypertension

NSAIDs, including etodolac tablets, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including etodolac tablets, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs.

Use of etodolac may blunt the CV effects of several therapeutic agents used to treat these medical conditions [e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs)] [see **DRUG INTERACTIONS**].

Avoid the use of etodolac tablets in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If etodolac tablets are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including etodolac tablets, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 - 6 months, and in about 2 - 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease, and/or gastrointestinal bleeding, and who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients, and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory 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 greater risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

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.

Caution is recommended in patients with pre-existing kidney disease.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of etodolac tablets in patients with advanced renal disease. Therefore, treatment with etodolac tablets is not recommended in these patients with advanced renal disease. If etodolac tablets therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDS, anaphylactoid reactions may occur in patients without prior exposure to etodolac tablets. Etodolac tablets should not be given to patients with the aspirin triad. This symptom complex 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 NSAIDs. Fatal reactions have been reported in such patients (see **CONTRAINDICATIONS** and **PRECAUTIONS, General, Pre-existing Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including etodolac tablets, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, the third trimester, as with other NSAIDs, etodolac tablets should be avoided because it may cause premature closure of the ductus arteriosus (see **PRECAUTIONS, Pregnancy, Nonteratogenic Effects**).

PRECAUTIONS

General

Etodolac tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered solely if a decision is made to discontinue corticosteroids.

The pharmacological activity of etodolac tablets in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including etodolac tablets. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable 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 NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure, some of them with fatal outcomes, have been reported.

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

Hematological Effects

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

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving etodolac tablets who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Pre-existing Asthma

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 tablets 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

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. **Cardiovascular Thrombotic Events**
   Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [see **Warnings**].
2. Etodolac tablets, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Gastrointestinal Effects-Risk of Ulceration, Bleeding, and Perforation**).
3. Etodolac tablets, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
4. **Heart Failure and Edema**
   Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [see **Warnings**].
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS**).
7. In late pregnancy, the third trimester, as with other NSAIDs, etodolac tablets should be avoided because they may cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile 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 or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, etodolac tablets should be discontinued.

Drug Interactions

ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors (see **WARNINGS**).

Antacids

The concomitant administration of antacids has no apparent effect on the extent of absorption of etodolac tablets. 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 tablets are 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.

Cyclosporine, Digoxin, 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 cyclosporine, digoxin, 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. NSAIDs, such as etodolac, should not be administered prior to or concomitantly with high doses of methotrexate. NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. In general, caution should be used when NSAIDs are administered concomitantly with methotrexate.

Diuretics

Etodolac has no apparent pharmacokinetic interaction when administered with furosemide or hydrochlorothiazide. Nevertheless, clinical studies, as well as postmarketing observations have shown that etodolac can reduce the natriuretic effect of furosemide and thiazides in some patients with possible loss of blood pressure control. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal insufficiency or failure (see **WARNINGS**, ***Renal Effects***), as well as to assure diuretic efficacy.

2 D Code

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Etodolac Tablets USP
400 mg/500 mg

DIMENSIONS : 280 X 450MM

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

Lithium
NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. Careful monitoring of lithium levels is advised in the event NSAID dosage adjustments are required.

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.

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

Warfarin
The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than that of users of either drug alone. Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and etodolac tablets 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 tablets as measured by prothrombin time. Thus, concomitant therapy with warfarin and etodolac should not require dosage adjustment of either drug. However, caution should be exercised because there have been a few spontaneous reports of prolonged prothrombin times, with or without bleeding, in etodolac-treated patients receiving concomitant warfarin therapy. Close monitoring of such patients is therefore recommended.

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

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dL were observed in arthritic patients receiving etodolac (600 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/m^2, respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in in vitro tests performed with S. typhimurium and mouse lymphoma cells as well as in an in vivo mouse micronucleus test. However, data from the in vitro human peripheral lymphocyte test showed an increase in the number of gaps (3.0 to 5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 µg/mL) compared to negative controls (2.0%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m^2). 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. Animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. Etodolac tablets should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Etodolac tablets should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use during pregnancy (particularly during the third trimester) should be avoided.

Labor and Delivery
In rat studies with NSAIDs, 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 tablets on labor and delivery in pregnant women are unknown.

Nursing Mothers
Trace amounts of some NSAIDs have been reported in human milk. 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 tablets, 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 below the age of 18 years have not been established.

Geriatric Use
As with any NSAID, caution should be exercised in treating the elderly (65 years and older) and when increasing the dose (see **WARNINGS**).

In etodolac tablets clinical studies, no overall differences in safety or effectiveness were observed between these patients and younger patients. In pharmacokinetic 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. Therefore, no dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics (see **CLINICAL PHARMACOLOGY**, **Special Populations**).

Elderly patients may be more sensitive to the antiprostaglandin effects of NSAIDs (on the gastrointestinal tract and kidneys) than younger patients (see **WARNINGS**). In particular, elderly or debilitated patients who receive NSAID therapy seem to tolerate gastrointestinal ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population.

Etodolac is eliminated primarily by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **WARNINGS**, ***Renal Effects***).

ADVERSE REACTIONS
In patients taking etodolac tablets or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1-10% of patients are:

Gastrointestinal experiences including: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal), vomiting.

Other events including: abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritis, rashes, tinnitus.

Adverse-reaction information for etodolac was derived from 2,629 arthritic patients treated with etodolac tablets 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*, abdominal distension, epigastric pain, abnormal stools, constipation, gastritis, melena, vomiting.

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

Skin and appendages—Pruritus, rash.

Special senses—Blurred vision, tinnitus.

Urogenital system—Dysuria, urinary frequency.

Musculoskeletal—Arthralgia.

*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, anaphylactic/anaphylactoid reactions (including shock).*

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, aplastic anemia, leukopenia, neutropenia, pancytopenia.

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

Nervous system—Insomnia, somnolence.

Respiratory system—Asthma, *pulmonary infiltration with eosinophilia.*

Skin and appendages—Angioedema, sweating, urticaria, exfoliative dermatitis, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome, toxic epidermal necrolysis, leukocytoclastic vasculitis,* **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, GI discomfort, burning sensation, blood in stools, gastralgia, upper abdominal discomfort.

Metabolic and nutritional—Change in weight.

Nervous system—Paresthesia, confusion, irritability.

Respiratory system— Bronchitis, bronchospasm, dyspnea, pharyngitis, rhinitis, sinusitis.

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

Special senses—Conjunctivitis, deafness, taste perversion, loss of taste.

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

Musculoskeletal—Muscle pain.

Additional Adverse Reactions Reported with NSAIDs

Body as a whole—Sepsis, death

Cardiovascular system—Tachycardia

Digestive system—Gastric ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis

Hemic and lymphatic system—Lymphadenopathy

Nervous system—Anxiety, dream abnormalities, convulsions, coma, hallucinations, meningitis, tremors, vertigo

Respiratory system—Respiratory depression, pneumonia

Urogenital system—Oliguria/polyuria, proteinuria

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. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic 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). Forced diuresis, alkalinization of the urine, hemodialysis, or hemoperfusion would probably not be useful due to etodolac's high protein binding.

DOSAGE AND ADMINISTRATION
Carefully consider the potential benefits and risks of etodolac tablets and other treatment options before deciding to use etodolac tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

After observing the response to initial therapy with etodolac tablets, the dose and frequency should be adjusted to suit an individual patient's needs.

Dosage adjustment of etodolac tablets 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 **WARNINGS**, ***Renal Effects***).

Analgesia
The recommended total daily dose of etodolac tablets for acute pain is up to 1000 mg, given as 200-400 mg every 6 to 8 hours. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled trials.

Osteoarthritis and Rheumatoid Arthritis
The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis or rheumatoid arthritis is: 300 mg b.i.d., t.i.d., or 400 mg b.i.d., or 500 mg b.i.d. A lower dose of 600 mg/day may suffice for long-term administration. 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 tablets USP, 400 mg are available as beige colored, oval shaped tablets debossed BY7 on one side and plain on other side.
- in bottles of 100 NDC 76385-118-01

Etodolac tablets USP, 500 mg are available as blue colored, oval shaped tablets debossed BY8 on one side and plain on other side.
- in bottles of 100 NDC 76385-119-01

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Store tablets in original container until ready to use.

Dispense in a tight, light-resistant container as defined in the USP, with a child resistant closure.

Manufactured by:
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Revised: 04/2021

Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach),stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:
- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called "corticosteroids", "anticoagulants", "SSRIs" or "SNRIs"
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

NSAIDs should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?
NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?
Do not take NSAIDs:
- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDS, tell your healthcare provider about all of your medical conditions, including if you:
- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. **You should not take NSAIDs after 29 weeks of pregnancy**
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?
- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:
- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:
- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.
These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs
- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the counter). Talk to your healthcare provider before using over the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
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Revised: 04/2021

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