

**ETODOLAC- etodolac tablet, film coated, extended release**  
**H.J. HARKINS COMPANY, INC.**

**Boxed warning**

Cardiovascular Thrombotic Events - WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS Cardiovascular Thrombotic Events Nonsteroidal ...

Cardiovascular Thrombotic Events

**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**

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 extended-release tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications and Warnings and Precautions ].

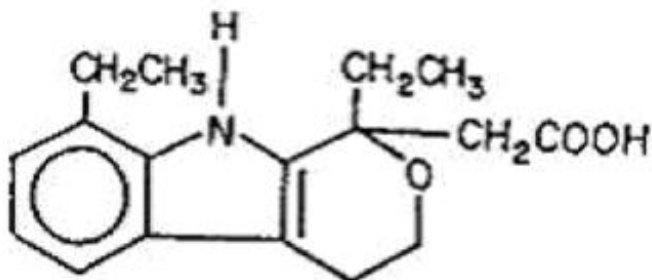
Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [see Warnings and Precautions].

**Description**

Etodolac extended-release tablets, USP contain etodolac, which is a member of the pyranocarboxylic acid group of non-steroidal 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 to off-white crystalline powder, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

The chemical name is ( $\pm$ ) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. It has the following structural formula:



C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub> M.W. 287.36

Each etodolac extended-release tablet, USP intended for oral administration contains 400 mg or 500 mg or 600 mg of etodolac. In addition, each tablet contains the following inactive ingredients: disodium

hydrogen phosphate, ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, talc, titanium dioxide and triacetin. Additionally each 400 mg tablet contains: D&C yellow # 10 aluminum lake, FD&C Red # 40 aluminum lake and FD&C yellow # 6 aluminum lake and each 500 mg tablet contains: FD&C Blue # 2 aluminum lake, iron oxide black and iron oxide yellow and each 600 mg tablet contains: FD&C blue # 2 aluminum lake, iron oxide red and iron oxide yellow.

The USP Drug Release test complies with USP Dissolution Test 1.

## Clinical Pharmacology

### Pharmacodynamics

Etodolac extended-release tablets are a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac extended-release tablets, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition.

### Pharmacokinetics

#### Absorption

Etodolac extended-release tablets and etodolac tablets both contain etodolac, but differ in their release characteristics. The systemic availability of etodolac from etodolac extended-release tablets is generally greater than 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. After oral administration of etodolac extended-release tablets in doses up to 800 mg once daily, peak concentrations occur approximately 6 hours after dosing and are dose proportional for both total and free etodolac.

Table 1 shows the comparison of etodolac pharmacokinetic parameters after the administration of etodolac tablets and etodolac extended-release tablets.

Table 2 shows the etodolac pharmacokinetic parameters in various populations. The data from patients with renal and hepatic impairment were obtained following administration of (immediate-release) etodolac tablets.

#### Table 1

Mean (CV)%\*

\*

% Coefficient of variation

#### Pharmacokinetic Parameters

Etodolac Tablets

Etodolac Extended-release Tablets

Extent of Oral Absorption (Bioavailability) [F]

≥ 80%

≥ 80%

Time to Peak Concentration (T<sub>max</sub>), h

1.4 (61%)

6.7 (47%)

Oral Clearance (CL/F), mL/h/kg

49.1 (33%)

46.8 (37%)

Apparent Volume of Distribution (V<sub>d</sub>/F), mL/kg

393 (29%)

566 (26%)

Terminal Half-Life (t<sub>1/2</sub>), h

6.4 (22%)

## 8.4 (30%)

Table 2 Mean (CV%)\* Pharmacokinetic Parameters of Etodolac in Normal Healthy Adults and Various Special Populations

Etodolac Extended-release Tablets

Etodolac Tablets

\* % Coefficient of variation

† Pharmacokinetic parameters obtained following administration of etodolac tablets

‡ Age range (years)

NA = not available

PK

Parameters

Normal

Healthy

Adults

Healthy

Males

Healthy

Females

Elderly

(> 65 yr)

Hemodialysis†

(24 to 65) (n = 9)

Renal

Impairment†

Hepatic

Impairment†

(18 to 44)‡

(n = 116)

(18 to 43)

(n = 102)

(25 to 44)

(n = 14)

(66 to 88)

(n = 24)

Dialysis On

Dialysis Off

(46 to 73)

(n = 10)

(34 to 60)

(n = 9)

T<sub>max</sub>, h

6.7 (47%)\*

6.8 (45%)

4.5 (56%)

6.2 (51%)

1.7 (88%)

0.9 (67%)

2.1 (46%)

1.1 (15%)

Oral Clearance,  
mL/h/kg (CL/F)

46.8 (37%)

46.8 (37%)

47.2 (38%)

51.6 (40%)

NA

NA

58.3 (19%)

42 (43%)

Apparent

Volume of

Distribution,

mL/kg (Vd/F)

566 (26%)

580 (26%)

459 (28%)

552 (34%)

NA

NA

NA

NA

Terminal Half-

Life, h

8.4 (30%)

8.4 (29%)

7.6 (45%)

7.8 (26%)

5.1 (22%)

7.5 (34%)

NA

5.7 (24%)

#### Food/Antacid Effects

Food has no significant effect on the extent of etodolac extended-release tablets absorption, however, food significantly increased C<sub>max</sub> (54%) following a 600 mg dose.

The extent of absorption of etodolac is not affected when etodolac is administered with antacid.

Coadministration, with an antacid, decreases the peak concentration reached by about 15 to 20% with no measurable effect on time-to-peak.

#### Distribution

The mean apparent volume of distribution (V<sub>d</sub>/F) of etodolac following administration of etodolac extended-release tablets is 566 mL/kg. Etodolac is more than 99% bound to plasma proteins, primarily to albumin, and is independent of etodolac 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.

#### Metabolism

Etodolac metabolites do not contribute significantly to the pharmacological activity of etodolac extended-release tablets.

Following administration of immediate-release etodolac, several 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  $^{14}\text{C}$ -etodolac, hydroxylated metabolites accounted for less than 10% of total drug in serum. On chronic dosing, hydroxylated-etodolac metabolites do 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 role, if any, of a specific cytochrome P450 system in the metabolism of etodolac is unknown. 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 etodolac extended-release tablets dosing is 47 ( $\pm 17$ ) mL/h/kg. The terminal half-life ( $t_{1/2}$ ) of etodolac after etodolac extended-release tablets administration is 8.4 hours compared to 6.4 hours for etodolac tablets. Approximately 1% of an etodolac tablet dose is excreted unchanged in the urine, with 72% of the dose excreted into the urine as parent drug plus metabolites:

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

Fecal excretion accounted for 16% of the dose.

### Special Populations

#### Geriatric

In clinical studies, age was not shown to have any effect on half-life or protein binding, and demonstrated no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, as they may be more sensitive to antiprostaglandin effects than younger patients (see PRECAUTIONS, GERIATRIC USE).

#### Pediatric

The pharmacokinetics of etodolac extended-release tablets were assessed in an open-label, 12 week clinical trial which included plasma sampling for population pharmacokinetics. Seventy-two (72) patients, 6 to 16 years of age, with juvenile rheumatoid arthritis, received etodolac extended-release tablets in doses of 13.3 to 21.3 mg/kg given as 400 to 1000 mg once daily. The results from a population pharmacokinetic analysis based on the 59 subjects who completed the trial are as follows:

Table 3 Pharmacokinetic Parameter Estimates for Etodolac Extended-release Tablets in Patients with Juvenile Rheumatoid Arthritis

Parameter

JRA\* (Age:6 to 16)† n = 59

\*

Mean (CV) of parameter estimates predicted from population pharmacokinetics

†

Age range (years)

Oral Clearance (CL/F), mL/h/kg

47.8 (38%)

Apparent Volume of Distribution (Vd/F), mL/kg

78.9 (61%)

Half-life (t<sub>1/2</sub>), h

12.1 (75%)

While similar, the pharmacokinetic parameters for children with juvenile rheumatoid arthritis did not directly correlate with adult pharmacokinetic data in rheumatoid arthritis. In the population pharmacokinetic analysis, body weights below 50 kg were found to correlate with CL/F (see DOSAGE AND ADMINISTRATION).

#### 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

The pharmacokinetics of etodolac following administration of etodolac extended-release tablets have not been investigated in subjects with hepatic insufficiency. Following administration of etodolac tablets, the plasma protein binding and disposition of total and free etodolac were unchanged in the presence of compensated hepatic cirrhosis. Although no dosage adjustment is generally required in patients with chronic hepatic diseases, etodolac clearance is dependent on liver function and could be reduced in patients with severe hepatic failure.

#### Renal Insufficiency

The pharmacokinetics of etodolac following administration of etodolac extended-release tablets have not been investigated in subjects with renal insufficiency. Etodolac renal clearance following administration of etodolac tablets was unchanged in the presence of mild-to-moderate renal failure (creatinine clearance, 37 to 88 mL/min). 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. Etodolac plasma protein binding decreases in patients with severe renal deficiency. Etodolac should be used with caution in such patients because, as with other NSAIDs, it may further decrease renal function in some patients. Etodolac is not significantly removed from the blood in patients undergoing hemodialysis.

## Clinical Studies

### Arthritis

The use of etodolac extended-release tablets in managing the signs and symptoms of osteoarthritis of the knee and rheumatoid arthritis was assessed in doubleblind, randomized, parallel, controlled clinical trials in 1552 patients. In these trials, etodolac extended-release tablets, given once daily, provided efficacy comparable to immediate-release etodolac.

The safety, efficacy, and pharmacokinetics of etodolac extended-release tablets were assessed in an open-label, 12 week clinical trial. Seventy-two (72) patients, 6 to 16 years of age, with juvenile rheumatoid arthritis, received etodolac extended-release tablets in doses of 400 to 1000 mg (13.3 to 21.3 mg/kg body weight) once daily. At these doses, etodolac extended-release tablets controlled the signs and symptoms of juvenile rheumatoid arthritis. Based on the results of this study, the safety profile of etodolac extended-release tablets (at doses not exceeding 20 mg/kg) appeared to be similar to that observed in the adult arthritic patients in clinical trials (see PRECAUTIONS, PEDIATRIC USE).

## Indications & Usage

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

WARNINGS).

Etodolac extended-release tablets, USP are indicated:

- \* For relief of signs and symptoms of juvenile arthritis
- \* For relief of the signs and symptoms of rheumatoid arthritis
- \* For relief of the signs and symptoms of osteoarthritis

### **contraindications**

Etodolac extended-release tablets are contraindicated in patients with known hypersensitivity to etodolac.

Etodolac extended-release tablets should not be given to patients who have experienced asthma, urticaria, or 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, PREEXISTING ASTHMA).

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

### Hypertension

NSAIDs, including etodolac extended-release tablets, can lead to onset of new hypertension or worsening of preexisting 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 extended-release 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 extended-release tablets in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If etodolac extended-release 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 extended-release 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 to 6 months, and in about 2 to 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.

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 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 greatest 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.

### Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of etodolac extended-release tablets in patients with advanced renal disease. Therefore, treatment with etodolac extended-release tablets is not recommended in these patients with advanced renal disease. If etodolac extended-release tablet 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 known prior exposure to etodolac extended-release tablets. Etodolac extended-release 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 (see CONTRAINDICATIONS and PRECAUTIONS, PREEXISTING ASTHMA). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

### Skin Reactions

NSAIDs, including etodolac extended-release 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, as with other NSAIDs, etodolac extended-release tablets should be avoided because it may cause premature closure of the ductus arteriosus.

## **Precautions**

### General

Etodolac extended-release 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 slowly if a decision is made to discontinue corticosteroids.

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

### Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including etodolac extended-release 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 extended-release 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 extended-release 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.

### Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, etodolac extended-release tablets should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting 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.

**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].

Etodolac extended-release 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).

Etodolac extended-release 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. 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].

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.

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).

In late pregnancy, as with other NSAIDs, etodolac extended-release tablets should be avoided because it will 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. 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 extended-release 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.

#### Aspirin

When etodolac extended-release 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 extended-release tablets and aspirin is not generally recommended because of the potential of increased adverse effects.

#### Cyclosporine and Digoxin

Etodolac extended-release tablets, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs, leading to elevated serum levels of cyclosporine and digoxin and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac extended-release tablets, 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.

#### Furosemide

Clinical studies, as well as post marketing observations, have shown that etodolac extended-release tablets can reduce the natriuretic effect of furosemide and thiazides in some patients. 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 failure (see WARNINGS, RENAL EFFECTS), as well as to assure diuretic efficacy.

#### 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.

## 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. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

## Phenylbutazone

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 coadministration of phenylbutazone, it is not recommended that they be coadministered.

## 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 users of either drug alone.

## 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 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

## Carcinogenesis, Mutagenesis, 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<sup>2</sup>, respectively) or less for periods of 18 months or 2 years, respectively. Etodolac was not mutagenic in in vitro tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an in vivo mouse micronucleus test. However, data from the in vitro human peripheral lymphocyte test showed an increase in the number of gaps (3% to 5% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 g/mL) compared to negative controls (2%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m<sup>2</sup>). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

## Pregnancy

### Teratogenic Effects

### Pregnancy category C

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

### Nonteratogenic Effects

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) 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 extended-release tablets on labor and delivery in pregnant women are unknown.

## Nursing Mothers

It is not known whether this drug 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 extended-release 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 6 years have not been established.

## Geriatric Use

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

## Adverse Reactions

A total of 1552 patients were exposed to etodolac extended-release tablets in controlled clinical studies of at least 4 weeks in length and using daily doses in the range of 400 to 1200 mg. In the tabulations below, adverse event rates are generally categorized based on the incidence of events in the first 30 days of treatment with etodolac extended-release tablets. As with other NSAIDs, the cumulative adverse event rates may increase significantly over time with extended therapy.

In patients taking NSAIDs, including etodolac extended-release tablets, the most frequently reported adverse experiences occurring in approximately 1 to 10% of patients are:

Gastrointestinal experiences including

abdominal pain

constipation

Diarrhea

dyspepsia

flatulence

GI ulcers (gastric/duodenal)\*

gross bleeding/perforation\*

nausea

Vomiting

Other events including:

\*

Adverse events that were observed in < 1% of patients in the first 30 days of treatment with etodolac extended-release tablets in clinical trials.

abnormal renal function\*

Anemia\*

asthenia

dizziness

edema\*

elevated liver enzymes\*

headaches

hypertension

increased bleeding time\*

infection

pharyngitis

pruritus

rashes

rhinitis

tinnitus\*

## Additional NSAID Adverse Experiences Reported Occasionally with NSAIDs or Etodolac Extended-release Tablets Include

### Body as a whole

Allergic reaction, anaphylactic/anaphylactoid reactions (including shock), chills, fever, sepsis

### Cardiovascular system

Congestive heart failure, flushing, palpitations, tachycardia, syncope, vasculitis (including necrotizing and allergic)

### Digestive system

Anorexia, cholestatic hepatitis, cholestatic jaundice, dry mouth, duodenitis, eructation, esophagitis, gastritis, gastric/peptic ulcers, glossitis, hepatic failure, hepatitis, hematemesis, intestinal ulceration, jaundice, liver necrosis, melena, pancreatitis, rectal bleeding, stomatitis

### Hemic and lymphatic system

Agranulocytosis, ecchymosis, eosinophilia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, purpura, thrombocytopenia

### Metabolic and nutritional

Hyperglycemia in previously controlled diabetic patients

### Nervous system

Anxiety, confusion, depression, dream abnormalities, insomnia, nervousness, paresthesia, somnolence, tremors, vertigo

### Respiratory system

Asthma, dyspnea, pulmonary infiltration with eosinophilia

### Skin and appendages

Angioedema, cutaneous vasculitis with purpura, erythema multiforme, hyperpigmentation, sweating, urticaria, vesiculobullous rash

### Special senses

Blurred vision, photophobia, transient visual disturbances

### Urogenital system

Dysuria, elevated BUN, oliguria/polyuria, proteinuria, renal failure, renal insufficiency, renal papillary necrosis, serum creatinine increase, urinary frequency

## Other NSAID Adverse Reactions, Which Occur Rarely Are

### Body as a whole

Anaphylactic reactions, appetite changes, death

### Cardiovascular system

Arrhythmia, cerebrovascular accident, hypotension, myocardial infarction

### Digestive system

Colitis, esophagitis with or without stricture or cardiospasm, thirst, ulcerative stomatitis

### Hemic and lymphatic system

Aplastic anemia, lymphadenopathy

### Metabolic and nutritional

Change in weight

Nervous system

Coma, convulsions, hallucinations, meningitis

Respiratory

Bronchitis, pneumonia, respiratory depression, sinusitis

Skin and appendages

Alopecia, exfoliative dermatitis, maculopapular rash, photosensitivity, skin peeling, Stevens-Johnson syndrome, toxic epidermal necrosis

Special senses

Conjunctivitis, deafness, hearing impairment, taste perversion

Urogenital system

Cystitis, hematuria, interstitial nephritis, leukorrhea, renal calculus, uterine bleeding irregularities

### **Overdosage**

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an 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, alkalization of the urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

### **Dosage and Administration**

Carefully consider the potential benefits and risks of etodolac extended-release tablets and other treatment options before deciding to use etodolac extended-release 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 extended-release tablets, the dose and frequency should be adjusted to suit an individual patient's needs.

#### **Juvenile Rheumatoid Arthritis**

For the relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 6 to 16 years of age, the recommended dose given orally once per day should be based on body weight, according to the following table:

Table 4

Body Weight Range (kg)

Dose

20 to 30

400 mg Tablet x 1

31 to 45

600 mg Tablet x 1

46 to 60

400 mg Tablet x 2

> 60

500 mg Tablet x 2

Rheumatoid Arthritis and Osteoarthritis

For the relief of the signs and symptoms of osteoarthritis or rheumatoid arthritis, the recommended starting dose of etodolac extended-release tablets is 400 to 1000 mg given orally once per day.

As with other NSAIDs, the lowest effective dose should be sought for each patient. In chronic conditions, a therapeutic response to therapy with etodolac extended-release tablets is sometimes seen within one week of therapy, but most often is observed by two weeks.

### **How Supplied**

Etodolac Extended-release Tablets USP, 400 mg are orange-colored, oval-shaped, beveled edged, film-coated tablets, debossed with "271" on one side and plain on other side and are supplied as follows:

NDC 68382-271-14 in bottles of 60 tablets

NDC 68382-271-01 in bottles of 100 tablets

NDC 68382-271-05 in bottles of 500 tablets

NDC 68382-271-10 in bottles of 1000 tablets

NDC 68382-271-77 in unit-dose blister cartons of 100 (10 x 10) unit dose tablets

Etodolac Extended-release Tablets USP, 500 mg are grey-colored, oval-shaped, beveled edged, film-coated tablets, debossed with "272" on one side and plain on other side and are supplied as follows:

NDC 68382-272-14 in bottles of 60 tablets

NDC 68382-272-01 in bottles of 100 tablets

NDC 68382-272-05 in bottles of 500 tablets

NDC 68382-272-10 in bottles of 1000 tablets

NDC 68382-272-77 in unit-dose blister cartons of 100 (10 x 10) unit dose tablets

Etodolac Extended-release Tablets USP, 600 mg are blue-colored, oval-shaped, beveled edged, film-coated tablets debossed with "273" on one side and plain on other side and are supplied as follows:

NDC 68382-273-14 in bottles of 60 tablets

NDC 68382-273-01 in bottles of 100 tablets

NDC 68382-273-05 in bottles of 500 tablets

NDC 68382-273-10 in bottles of 1000 tablets

NDC 68382-273-77 in unit-dose blister cartons of 100 (10 x 10) unit dose tablets

Storage:

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

Protect from excessive heat and humidity.

Dispense in a tight, light-resistant container with a child-resistant closure.

### **SPL Unclassified section**

manufactured by:



Cadila Healthcare Ltd.

Ahmedabad, India

Distributed by:

Zydus Pharmaceuticals USA Inc.

Pennington, NJ 08534

Rev.: 06/16

**Package label**

		<small>CAUTION: Federal Law PROHIBITS the transfer of this drug to anyone other than the person whom prescribed and prohibits dispensing without a prescription, unless OTC. See outsert for add'l Rx info KEEP OUT OF REACH OF CHILDREN Store in a cool, dry place at 68° - 77° F unless printed otherwise.</small>
<p>52959-0649-15 ETODOLAC E.R. 500mg TAB #15 Compare: Lodine XL Exp. 04/19 Lot#: EAC11ZY5AV Mfg. ZYDUS 68382-0272-01 Account: 00-8101</p>		<p>ETODOLAC E.R. 500MG TAB NDC:52959-0649-15 QTY:#15 EXP: 04/19 LOT:EAC11ZY5AV 68382-0272-01</p>
<p>Take as directed by your Physician.</p>		<p>ETODOLAC E.R. 500MG TAB NDC:52959-0649-15 QTY:#15 EXP: 04/19 LOT:EAC11ZY5AV 68382-0272-01</p>
		<p>ETODOLAC E.R. 500MG TAB NDC:52959-0649-15 QTY:#15 EXP: 04/19 LOT:EAC11ZY5AV 68382-0272-01</p>
		<p>ETODOLAC E.R. 500MG TAB NDC:52959-0649-15 QTY:#15 EXP: 04/19 LOT:EAC11ZY5AV 68382-0272-01</p>
		<p>000AAD6C0000 Repack: H.J. Harkins Co., Inc. Grover Beach, CA 93433</p>

**Pakage Label**



CAUTION: Federal Law PROHIBITS the transfer of this drug to anyone other than the person whom prescribed and prohibits dispensing without a prescription, unless OTC. See outsort for add'l Rx info  
KEEP OUT OF REACH OF CHILDREN Store in a cool, dry place at 68° - 77° F unless printed otherwise.

52959-0649-30

ETODOLAC E.R. 500mg TAB #30  
Compare: Lodine XL  
Exp. 04/19 Lot#: EAC11ZY5AW  
Mfg. ZYDUS 68382-0272-01  
Account: 00-8101

ETODOLAC E.R. 500MG TAB  
NDC:52959-0649-30 QTY:#30  
EXP: 04/19 LOT:EAC11ZY5AW  
68382-0272-01

ETODOLAC E.R. 500MG TAB  
NDC:52959-0649-30 QTY:#30  
EXP: 04/19 LOT:EAC11ZY5AW  
68382-0272-01

ETODOLAC E.R. 500MG TAB  
NDC:52959-0649-30 QTY:#30  
EXP: 04/19 LOT:EAC11ZY5AW  
68382-0272-01

ETODOLAC E.R. 500MG TAB  
NDC:52959-0649-30 QTY:#30  
EXP: 04/19 LOT:EAC11ZY5AW  
68382-0272-01

000A0D6B0000

Repack: H.J. Harkins Co., Inc. Grover Beach, CA 93433

Take as directed by your  
Physician.

## ETODOLAC

etodolac tablet, film coated, extended release

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:52959-649
Route of Administration	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ETODOLAC (UNII: 2M36281008) (ETODOLAC - UNII:2M36281008)	ETODOLAC	500 mg

### Product Characteristics

Color	gray	Score	score with uneven pieces
Shape	OVAL	Size	18mm
Flavor		Imprint Code	272
Contains			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52959-649-15	15 in 1 VIAL; Type 0: Not a Combination Product	03/06/2017	
2	NDC:52959-649-30	30 in 1 VIAL; Type 0: Not a Combination Product	03/06/2017	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091134	03/06/2017	

**Labeler** - H.J. HARKINS COMPANY, INC. (147681894)

## Establishment

Name	Address	ID/FEI	Business Operations
HJ Harkins Company, Inc.		147681894	manufacture(52959-649) , relabel(52959-649)

Revised: 7/2017

H.J. HARKINS COMPANY, INC.