TOLDIN 400

Etodolac I.P. 400mg

COMPOSITION

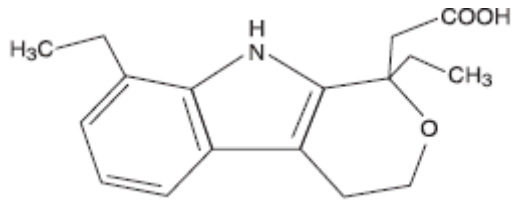
Each film coated tablet contains:
Etodolac I.P. 400mg
Colours: Yellow Oxide of Iron and Titanium dioxide I.P.

DESCRIPTION

TOLDIN is a combination product containing etodolac, a nonsteroidal antiinflammatory drug (NSAID) with analgesic and antipyretic properties.

Etodolac is a member of the pyranocarboxylic acid group of non-steroidal anti-inflammatory drugs (NSAIDs). Etodolac is a racemic mixture of [+] S and [-] R-enantiomers. Etodolac is a white or almost white, crystalline powder, soluble in ethanol (95 per cent), in chloroform, dimethylsulphoxide, in aqueous polyethylene and in glycol; practically insoluble in water. The chemical name is 1,8-diethyl-1,3,4,9-tetra hydropyrano-[3,4-b]indole-1-acetic acid. It has a pKa of 4.65 and an n-octanol: water partition coefficient of 11.4 at pH 7.4. The empirical formula is C17H21NO3 and its molecuar weight is 287.4.

It has the following structural formula:



PHARMACOLOGY

Pharmacodynamics
Etodolac is a 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, reported to be a preferential inhibitor ofcyclo-oxygenase 2 (COX-2).

Etodolac is a chiral compound given as the racemate. Peak plasma concentrations of the active (S) - enantiomer and of the inactive (R)-enantiomer are usually obtained within about 2 hours of a dose by mouth but plasma concentrations of the (R)-enantiomer have been reported to greatly exceed those of the (S)-enantiomer. Both enantiomers are highly bound to plasma proteins. Both are also distributed to the synovial fluid, although the difference in their concentrations may not be as marked as the difference in plasma concentrations. The plasma half-life of total etodolac has been reported to be

about 7 hours; excretion is mainly in the urine as hydroxylated metabolites and glucuronide conjugates; some may be excreted in the bile.

INDICATIONS

For the relief of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis

CONTRAINDICATIONS

Etodolac is contraindicated in patients with known hypersensitivity to etodolac.Etodolac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs and history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.Etodolac is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. Etodolac should not be used in patients with severe heart failure, hepatic failure and renal failure. Etodolac should not be used in patients with active or history of recurrent peptic ulceration or a history of peptic ulcer disease (with two or more distinct episodes of proven ulceration or bleeding). During the last trimester of pregnancy.

Cardiovascular Risk

NSAIDs[1] may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors forcardiovascular disease may be at greater risk.

Etodolac tablets are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

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.

[1] Throughout this package insert, the term NSAID refers to a non-aspirin non-steroidal anti-inflammatory drug.

SPECIAL PRECAUTIONS

General

Etodolac 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 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. 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 should be discontinued.

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs including etodolac. 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, 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 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 patientswith aspirinsensitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, etodolac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

Information for Patients Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy.
Etodolac, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up. Etodolac, 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 symptomsof 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. Etodolac, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, Stevens - Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which may result in hospitali-zations 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.

Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians. 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. In late pregnancy, the third trimester, as with other NSAIDs, etodolac should be avoided because it 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 should be discontinued.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m2, respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in in vitro tests performed with S. typhimurium and mouse lymphoma cells as well as in an in vivo mouse micronucleus test. However, data from the in vitro human peripheral lymphocyte test showed an increase in the number of gaps (3.0 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/m2). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

Warnings

Hypertension

NSAIDs, including etodolac, 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, 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.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Etodolac should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects -Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including etodolac, 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, anticoagulants such as warfarin, selective serotoninreuptake inhibitors or anti-platelet agents such as aspirin, 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 should0 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. NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematous (SLE) and mixed connective tissue disorders there maybe an increased risk of aseptic meningitis.

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 preexisting kidney disease.

Advanced Renal Disease
No information is available from controlled clinical studies regarding the use of etodolac in patients with advanced renal disease. Therefore, treatment with etodolac is not recommended in these patients with advanced renal disease. If etodolac 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. Etodolac 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. Emergency help should be sought in cases where an anaphy lactoid reaction occurs.

Respiratory disorders
Caution is required if etodolac is administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Skin Reactions
NSAIDs, including etodolac, can cause serious skin adverse events such as exfoliative dermatitis, SJS, and 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.

Impaired female fertility
The use of etodolac may impair female fertility and is not recommended in woman attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of Infertility, withdrawal of etodolac should be considered.

Pregnancy
In late pregnancy, the third trimester, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus.

DRUG INTERACTIONS
Since etodolac is extensively protein-bound, it may be necessary to modify the dosage of other highly proteinbound drugs.

ACE-inhibitors : Reports suggest that NSAIDs may diminish the antihypertensive effect of ACEinhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

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

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

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. NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. 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 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.

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. 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, as well as to assure diuretic efficacy. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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 lithiumclearance. 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.

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 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.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) Increased risk of gastrointestinal bleeding.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is a evidence of an increased risk of haemarthroses and haemtoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen. Bilirubin tests can give a false positive result due to the presence of phenolic metabolites of Etodolac in the urine.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

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.

ADVERSE EFFECTS
Etodolac: In patients taking etodolac 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, epigastric pain, indigestion, heart burn, ulcerative stomatitis, haematemesis, melaena, rectal bleeding, exacerbation of colitis, vasculitis, Other events including:
abnormal renal function, anemia, fatigue, weakness/malaise, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritis, rashes, tinnitus, abnormal vision, pyrexia, drowsiness, bilirubinuria, hepatic function abnormalities, Crohn's disease.

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephritic syndrome and renal failure.

Hepatic: abnormal liver function, hepatitis and jaundice Neurological and special senses: Visual disturbances, optic neuritis, headaches, paraethesia, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematous, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomitiong, fever or disorientation, depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Dermatological: Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare), photosensitivity. 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*, constipation, gastritis, melena, vomiting
Nervous system-Asthenia/malaise*, dizziness*, depression, nervousness, paraesthesia
Skin and appendages-Pruritus, rash Special senses-Blurred vision, tinnitus

Urogenital system-Dysuria, urinary frequency

*Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac. Drug-related patient-complaints occurring in fewer than 3%, but more than 1%, are unmarked. Incidence Less Than 1%-Probably Causally Related
(Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized.)
Body as a whole-Allergic reaction, anaphylactic/anaphylactoid reactions (including shock)

Cardiovascular system-Hypertension, congestive heart failure, cardiac failure, arterial thrombotic events (myocardial infarction or stroke), oedema, flushing, palpitations, syncope, vasculitis (including necrotizing and allergic),

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

Hemic and lymphatic system-Ecchymosis, anemia, thrombocytopenia, bleeding time increased, agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia
Metabolic and nutritional-Edema, serum creatinine increase, hyperglycemia in previously controlled diabetic patients

Nervous system-Insomnia, somnolence

Respiratory system-Asthma, aggravated asthma, bronchospasm, pulmonary infiltration with eosinophilia

Skin and appendages- Angioedema, sweating, urticaria, purpurea, exfoliative and bullous dermatoses, vesiculobullous rash, cutaneous vasculitis with purpura, Stevens-Johnson Syndrome, toxic epidermal necrolysis, hyperpigmentation, erythema multiforme.

Special senses- Photophobia, transient visual disturbances.

Urogenital system- Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis. Incidence Less Than 1%-Causal Relationship Unknown
(Medical events occurring under circumstances where causal relationship to etodolac is uncertain, these reactions are listed as alerting information for physicians.)

Body as a whole- Infection, headache

Cardiovascular system- Arrhythmias, myocardial infarction, cerebrovascular accident

Digestive system- Esophagitis with or without stricture or cardiospasm, colitis

Metabolic and nutritional- Change in weight

Nervous system- Paresthesia, confusion

Respiratory system- Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis

Skin and appendages- Alopecia, maculopapular rash, photosensitivity, skin peeling

Special senses- Conjunctivitis, deafness, taste perversion

Urogenital system- Cystitis, hematuria, leukorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities

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

(a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointaestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

(b) Therapeutic measure

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered.

Alternatively, in adults, gastric lavage should be considered within one hour of indigestion of a potentially lifethreatening overdose. Good urine output should be ensured. Renal and liver function should be closely montored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition. The standard practices of gastric lavage, activated charcoal administration and general supportive therapy should be undertaken.

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. 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. Etodolactablets should be used with caution in such patients, because, as with other NSAIDs, they may further decrease renal function in some patients with impaired renal function. 1 tablet 2 to 3 times daily depending on patient’s requirement for analgesia. It can be taken preferably with or after food.

The maximum dose of Toldin should not be exceeded the individual components maximal dose.

SPECIAL POPULATION

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 wellcontrolled studies in pregnant women. Etodolac should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic Effects Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern.

Etodolac 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 on labor and delivery in pregnant women are unknown.

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

Pediatric Use
Safety and effectiveness in pediatric patients 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.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. Elderly patients may be more sensitive to the antiprostaglandin effects of NSAIDs (on the gastrointestinal tract and kidneys) than younger. 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.

Expiry date
Do not use later than the date of expiry.

Storage
Store in a Dry Place at a Temperature Not Exceeding 25°C, Protected From Light.

Presentation
TOLDIN 400 is available as Blister strip of 10 Tablets

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
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Revised May 2013