For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

TOLDIN ER 600

1. Generic Name

Etodolac Extended-Release Tablets I.P.

2. Qualitative and quantitative composition

Each film coated extended-release tablet contains:

Etodolac I.P..... 600 mg

Excipients…..... q.s.

Colours: Yellow Oxide of Iron and Titanium Dioxide I.P.

The excipients used are Methocel, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Talcum, Colloidal Silicon Dioxide and Magnesium Stearate.

3. Dosage form and strength

Film Coated Extended-Release Tablets 600 mg.

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of Osteoarthritis and Rheumatoid Arthritis.

4.2 Posology and method of administration

For oral administration.

To be taken preferably with or after food

Undesirable effects may be minimised by using the shortest duration necessary to control symptoms.

Dosage: As directed by the Physician.

Direction for use: Tablet should be swallowed whole & not to be broken, chewed or crushed.

Adults

One tablet daily, taken with a glass of water.

Toldin ER 600 mg tablets must be swallowed whole.

The safety of doses in excess of 600 mg per day has not been established. No occurrence of tolerance or tachyphylaxis has been reported.

Elderly

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Children

Use in children is not recommended.

4.3 Contraindications

- Hypersensitivity to etodolac or to any of the excipients.
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angiooedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
- History of gastrointestinal bleeding or perforation, related to previous NSAID's therapy.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe heart failure, hepatic failure and renal failure
- During the last trimester of pregnancy

4.4 Special warnings and precautions for use

The use of Toldin ER 600 mg tablets with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Although non-steroidal anti-inflammatory drugs do not have the same direct effects on platelets as aspirin, all drugs which inhibit the biosynthesis of prostaglandins may interfere, to some extent, with platelet function. Patients receiving Toldin ER 600 mg Tablets who may be adversely affected by such actions should be carefully observed.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation, which may be fatal.

Cardiovascular, Renal and Hepatic Impairment:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients and the dose should be kept as low as possible. However, impairment of renal or hepatic functions due to other causes may alter drug metabolism; patients receiving concomitant long term therapy, especially the elderly, should be observed for potential side effects and their drug doses adjusted as needed, or the drug discontinued.

Patients on long-term treatment with Toldin ER 600 mg Tablets should be regularly reviewed as a precautionary measure e.g. for changes in renal function, haematological parameters, or hepatic function.

Cardiovascular and cerebrovascular effects:

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for Etodolac.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be

treated with Etodolac after careful consideration. Similar consideration should be made before initiating longterm treatment of patients with risk factors for cardiovascular disease (e.g hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Dermatological:

Serious skin reaction some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported very rarely in association with the use of NSAID's. Patients appear to be at highest risk of these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Etodolac ER tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other signs of hypersensitivity.

Respiratory disorders:

Caution is required if Toldin ER 600 mg Tablets are administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Impaired female fertility:

The use of Toldin ER 600mg tablet may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Toldin ER 600mg tablet should be considered.

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particular if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available.

Combination therapy with protective agents (e.g. misoprostal or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin or other drugs likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants. such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin.

When GI bleeding or ulceration occurs in patients receiving Etodolac, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

4.5 Drugs interactions

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding. Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin.

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

The concomitant administration of warfarin and Toldin ER 600 mg Tablets should not require a dosage adjustment of either drug, however it has rarely led to prolonged prothrombin times, therefore caution should be exercised when Toldin ER 600 mg Tablets are administered with warfarin.

Bilirubin tests can give a false positive result due to the presence of phenolic metabolites of etodolac in the urine.

Care should also be taken in patients treated with any of the following drugs as interactions have been reported in some patients including increase in serum levels of these compounds and associated toxicities:

Anti-hypertensives: Reduced anti-hypertensive effect.

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

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.

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.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Cyclosporin: Increased risk of nephrotoxity.

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 evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy:

Drugs which inhibit prostaglandin biosynthesis may cause dystocia and delayed parturition as evidenced by studies in pregnant animals.

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. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed, and the duration increased with an increased bleeding tendency in both mother and child. NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

4.7 Effects on ability to drive and use machines.

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms, and GI and cardiovascular risks below.

Gastrointestinal:

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Hypersensitivity:

Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular and cerebrovascular:

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of some NSAID's (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction of stroke). Other adverse reactions reported less commonly include:

Endocrine disorders:

Oedema, pyrexia

Musculoskeletal connective tissue and bone disorders:

Weakness/malaise

Respiratory, thoracic and mediastinal disorders:

Dyspnoea

Neurological and special senses:

Visual disturbances, optic neuritis, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation, depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue, tremor, insomnia, and drowsiness.

Dermatological:

Bullous reactions including Stevens-Johnson syndrome, and Toxic Epidermal Necrolysis (very rare). Photosensitivity.

Haematological:

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

Hepatic:

Abnormal liver function, hepatitis and jaundice.

Renal:

Bilirubinuria, urinary frequency, dysuria, nephrotoxicity in various forms including interstitial nephritis, nephrotic syndrome, renal failure.

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com

4.9 Overdose

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, and 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 ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

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.

5. Pharmacological properties

5.1 Mechanism of Action

All non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to inhibit the formation of prostaglandins. It is this action which is responsible both for their therapeutic effects and some of their side effects. The inhibition of prostaglandin synthesis observed with etodolac differs from that of other NSAIDs.

5.2 Pharmacodynamic properties

Inhibition of prostaglandin synthesis and COX-2 selectivity: All non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to inhibit the formation of prostaglandins. It is this action which is responsible both for their therapeutic effects and some of their side effects. The inhibition of prostaglandin synthesis observed with etodolac differs from that of other NSAIDs.

In an animal model at an established anti-inflammatory dose, cytoprotective PGE concentration in the gastric mucosa have been shown to be reduced to a lesser degree and for a shorter period than other NSAIDs. This finding is consistent with subsequent in-vitro studies which have found etodolac to be selective for induced cyclo-oxygenase 2 (COX-2, associated with inflammation) over COX-1 (cytoprotective).

Furthermore, studies in human cell models have confirmed that etodolac is selective for the inhibition of COX-2.

The clinical benefit of preferential COX-2 inhibition over COX-1 has yet to be proven. Anti-inflammatory effects: Experiments have shown etodolac to have marked anti-inflammatory activity, being more potent than several clinically established NSAIDs.

5.3 Pharmacokinetic properties

In man, etodolac is well absorbed following oral administration. Etodolac is highly bound to serum proteins.

The elimination half-life averages seven hours in man. The primary route of excretion is in the urine, mostly in the form of metabolites.

In subjects receiving daily doses of Toldin ER 600 mg Tablets to steady state levels over a three-day period, the peak plasma concentrations was 11.9 μg/ml at 7.8 hours.

6. Nonclinical properties

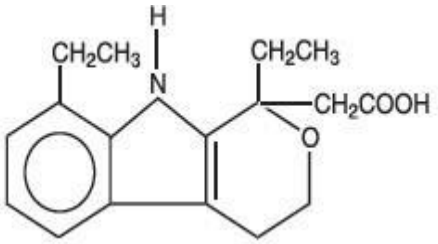
6.1 Animal Toxicology or Pharmacology

Preclinical data reveal no special hazard based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

7. Description

Toldin ER 600 Tablets contain etodolac, which is a member of the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Etodolac is white crystalline

compound, soluble in Ethanol (95%), in chloroform, in dimethylsulphoxide, in propylene glycol; practically insoluble in water. The chemical name is (±) 1, 8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The molecular weight is 287.37. Its molecular formula is $C_{17}H_{21}NO_3$ and it has the following structural formula:



Toldin ER Tablets are yellow coloured, capsule shaped, biconvex film coated extended release tablets having scored on one side. The excipients used are Methocel, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Talcum, Colloidal Silicon Dioxide and Magnesium Stearate.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Toldin ER 600 is packed in blister strips of 10 tablets.

8.4 Storage and handing instructions.

Store protected from light and moisture, at a temperature not exceeding 30^0C.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10. Details of manufacturer

Ravenbhel Healthcare Pvt Ltd.,

16-17, EPIP, SIDCO, Kartholi,

Bari-Brahmana, Jammu-181133

11. Details of permission or licence number with date

JK/01/56 issued on 28.10.2009.

12. Date of revision

MAR 2026

MARKETED BY

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