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

CLOTAN

1. Generic Name

Tolfenamic Acid Capsules 200 mg

2. Qualitative and quantitative Composition:

Each hard gelatin capsule contains:

Tolfenamic acid B.P…….200mg

(Sodium Methyl paraben I.P. used as preservative)

Approved colours used in hard gelatin capsule shells.

The excipients used are Starch, Lactose, Polyethylene glycol 6000, Povidone, Talc, Hard gelatin capsule Maroon/Yellow.

3. Dosage form and strength

Dosage form: Hard Gelatin Capsule

Strength: 200 mg

4. Clinical particulars

4.1. Therapeutic indication

Rheumatoid arthritis, osteo arthritis, ankylosing spondylitis and related conditions associated with pain. Additional indication of migraine.

4.2. Posology and method of administration

Posology

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

ADULTS

Migraine - acute attacks:200mg when the first symptoms of migraine appear. The treatment can be repeated once after 1-2 hours if a satisfactory response is not obtained.

CHILDREN

A paediatric dosage regimen has not yet been established.

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.

Method of administration

For oral administration. To be taken preferably with or after food.

4.3. Contraindications

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

4.4. Special warnings and precautions for use

In all patients:

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

The use of Tolfenamic acid with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Elderly:

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

Respiratory disorders:

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

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.

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 Tolfenamic acid.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Tolfenamic acid after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

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 GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly 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. misoprostol 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 Tolfenamic acid, 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 these conditions may be exacerbated.

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.

Dermatological:

Serious skin reactions, 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 NSAIDs. Patients appear to be at highest risk for 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. Tolfenamic acid should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Impaired female fertility:

The use of Tolfenamic acid 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 Tolfenamic acid should be considered.

Preclinical Safety Data

The therapeutic index for Tolfenamic acid is high, and gastrointestinal ulceration and kidney changes have only been seen with oral doses approximately 6-10 times the maximum therapeutic dose recommended for Tolfenamic acid. In human volunteers, Tolfenamic acid did not affect renal function

4.5. Drugs interactions

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.

Anti-hypertensives:

Reduced anti-hypertensive effect.

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:

The effect of lithium may be increased due to decreased elimination of lithium.

Methotrexate:

Decreased elimination of methotrexate.

Ciclosporin:

Increased risk of nephrotoxicity.

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.

Anti-coagulants:

NSAIDs may enhance the effects of anti-coagulants, such as warfarin. In patients treated with anti-coagulants, close monitoring of blood coagulation is recommended.

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.

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 haemarthrosis 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:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, tolfenamic acid should not be given unless clearly necessary. If tolfenamic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to: cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension) renal dysfunction, which may progress to renal failure with oligo-hydroamniosis the mother and the neonate, at the end of the pregnancy, to:possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses inhibition of uterine contractions resulting in delayed or prolonged labour. Consequently, tolfenamic acid is contraindicated during the third trimester of pregnancy.

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

Tolfenamic acid is well tolerated at the recommended dosage.

The following side effects have been observed:

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 NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke)

Other adverse reactions reported less commonly include:

Renal:

Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure. Harmless dysuria in the form of smarting during urination may occur occasionally, most commonly in males. The occurrence is correlated with the concentration of a metabolite and is most probably due to a local irritating effect of the urethra. Increased consumption of liquid or reduction of the dose diminishes the risk of smarting. The urine may, due to coloured metabolites, become a little more lemon coloured.

Hepatic:

Abnormal liver function, hepatitis and jaundice.

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, tremor, euphoria, 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).

Reporting of adverse reactions

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

Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal 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.

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

Tolfenamic acid is a prostaglandin synthesis inhibitor and a leukotriene synthesis inhibitor.

5.2. Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and ant rheumatic products, ATC code: M01AG02. NSAID with anti-inflammatory, analgesic, and antipyretic effects..

5.3. Pharmacokinetic properties

Tolfenamic acid is absorbed quickly and almost completely after oral administration. Hepatic first pass metabolism is as low as 15% (bioavailability 85%). Maximum plasma concentrations are reached after about 1-1½ hours. The half-life in plasma is about 2 hours. Tolfenamic acid is extensively bound to plasma proteins (99%). It is metabolised in the liver and tolfenamic acid as well as the metabolites is conjugated with glucuronic acid. About 90% of a given dose of tolfena-mic acid is excreted in the urine as glucuronic acid conjugates, and about 10% is excreted in the faeces. Enterohepatic circulation exists.

6. Nonclinical properties

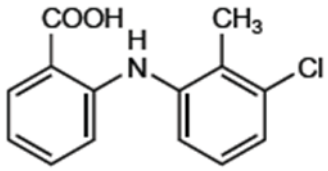
6.1. Animal Toxicology or Pharmacology

The therapeutic index for tolfenamic acid is high, and gastrointestinal ulceration and kidney changes have only been seen with oral doses approximately 6-10 times the maximum

therapeutic dose recommended for tolfenamic acid. In human volunteers, tolfenamic acid did not affect renal function.

7. Description

Chemically it is N-(3-Chloro-o-tolyl) anthranilic acid, empirical formula is $C_{14}H_{12}ClNO_2$ and molecular weight is 261.7. Its structure is



Tolfenamic capsule is Maroon/Yellow coloured, size '2' hard gelatin capsules printed "Torrent logo" (square emblem only) on body containing white powder. The excipients used are Starch, Lactose, Polyethylene glycol 6000, Povidone, Talc, Hard gelatin capsule Maroon/Yellow.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

Clotan is available in Blister pack of 10 Capsules.

8.4. Storage and handing instructions

Store in a cool, dry place. Protect from light. Keep out of reach of children.

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

Manufactured By:

Pure and Cure Healthcare Pvt Ltd

Plot No. 26A-30, Sector – 8A, IIE, SIDCUL,

Ranipur, Haridwar – 249403 (Uttarakhand).

11. Details of permission or licence number with date

Mfg Lic No.: 31/UA/2013 issued on 28.08.2014

12. Date of revision

FEB 2026

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/CLOTAN 200 mg/Feb-26/03/PI