xxxxxxxx-8883

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

ACEDOL

(Aceclofenac Tablets 100 mg)

(with β-Cyclodextrin)

COMPOSITION

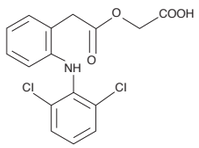
Each uncoated tablet contains :

Aceclofenac B.P. 100 mg

(with β-Cyclodextrin)

DESCRIPTION

Acedol is available as an immediate release tablets of Aceclofenac 100mg for oral administration. Chemically, Aceclofenac is (2-{(2,6-dichlorophenyl)amino} Phenyl acetooxyacetic acid). The empirical formula is $C_{16}H_{13}Cl_2NO_4$ and its molecular weight is 354.2.



PHARMACOLOGY

Aceclofenac is an orally effective NSAID of the phenylacetic acid group, which has anti-inflammatory and analgesic actions. The mode of action of Aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

Aceclofenac provides symptomatic relief in a variety of clinical conditions associated with pain and inflammation. Efficacy of Aceclofenac is comparable to other NSAIDs with regard to relief of pain and control of inflammation. Aceclofenac has favourable gastro-intestinal tolerance profile. The analgesic effect of Aceclofenac on the pain induced experimentally by chemical and mechanical stimuli was nearly equal to that of Indomethacin and Diclofenac. In patients with osteoarthritis of knees, Aceclofenac decreases pain, reduces disease severity and improves functional capacity of the knee. Aceclofenac reduces joint inflammation, pain and the duration of morning stiffness in patients with rheumatoid arthritis. The duration of morning stiffness and pain are reduced and spinal mobility improved by Aceclofenac in patients with ankylosing spondylitis. Aceclofenac is also effective in painful conditions in dental and gynaecological practice.

Pharmacokinetics

After oral administration, Aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 L. The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein-bound >99%. Aceclofenac circulates mainly as unchanged drug. 4'-Hydroxyaceclofenac is the main metabolite detected in plasma. Approximately two-thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites. No changes in the pharmacokinetics of aceclofenac have been detected in the elderly.

SPECIAL POPULATION

Renal insufficiency

There is no evidence that the dosage of Aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDs caution should be exercised.

Hepatic insufficiency

There is some evidence that the dose of Aceclofenac should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100 mg be used.

DRUG INTERACTION

Lithium: Aceclofenac, like many NSAIDs, may increase plasma concentrations of lithium.

Cardiac Glycosides: Through their renal effects, NSAIDs may increase plasma glycoside (including digoxin) levels, exacerbate cardiac failure and reduce the glomerular filtration rate in patients receiving glycosides.

Diuretics: Aceclofenac, like other NSAIDs, may inhibit the activity of diuretics. Although it was not shown to affect blood pressure control when co-administered with bendrofluazide, interactions with other diuretics cannot be ruled out. When concomitant administration with potassium-sparing diuretics is employed, serum potassium should be monitored. Diuretics can increase the risk of nephrotoxicity of NSAIDs

Anticoagulants: Like other NSAIDs, Aceclofenac may enhance the activity of anticoagulants. Close monitoring of patients on combined anticoagulant and Aceclofenac therapy should be undertaken.

Antidiabetic agents: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents with influencing their clinical effect. However, there have been isolated reports of hypoglycemic and hyperglycemic effects. Thus with Aceclofenac, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

Methotrexate: Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase plasma levels, resulting in increased toxicity.

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

Other NSAIDs and steroids: Concomitant therapy with aspirin, other NSAIDs and steroids may increase the frequency of adverse reactions, including the risk of GI bleeding.

Cyclosporin: Cyclosporin nephrotoxicity may be increased by the effect of NSAIDs on renal prostaglandins.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving a NSAIDs.

INDICATIONS

Acedol is indicated for relief of pain and inflammation in Osteoarthritis, Rheumatoid Arthritis and Ankylosing Spondylitis.

CONTRAINDICATIONS

NSAIDs should not be administered to patients with a history of or active or suspected peptic ulcer or gastro-intestinal bleeding.

Acedol should not be given to patients with moderate to severe renal impairment.

Acedol should not be prescribed during pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.

Acedol should not be administered to patients previously sensitive to aceclofenac or in whom aspirin or NSAIDs precipitate attacks of asthma, acute rhinitis or urticaria or who are hypersensitive to these drugs. Acedol is contraindicated in cases where there is hypersensitivity to any of its constituents.

WARNINGS

Gastro-intestinal: Close medical surveillance is imperative in patients with symptoms indicative of gastro-intestinal disorders, with a history suggestive of gastro-intestinal ulceration, with ulcerative colitis or with Crohn's disease, bleeding diathesis or haematological abnormalities.

Gastro-intestinal bleeding or ulcerative perforation, haematemesis and melaena have in general more serious consequences in the elderly. They can occur at any time during treatment, with or without warning symptoms or a previous history. In the rare instances where gastro-intestinal bleeding or ulceration occurs in patients receiving Aceclofenac, the drug should be withdrawn.

Hepatic: Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function.

Hypersensitivity reactions: As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

PRECAUTIONS

Renal: Patients with mild renal or cardiac impairment and the elderly should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored regularly.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Aceclofenac.

Hepatic: If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Aceclofenac should be discontinued. Hepatitis may occur without prodromal symptoms.

Use of Aceclofenac in patients with hepatic porphyria may trigger an attack.

Haematological: Aceclofenac may reversibly inhibit platelet aggregation.

Cardiovascular: NSAIDs should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with

NSAIDs administration.

Long-term treatment: All patients who are receiving NSAIDs should be monitored as a precautionary measure e.g. renal failure hepatic function (elevation of liver enzymes may occur) and blood counts.

Use with caution: In patients suffering from or with a history of bronchial asthma since NSAIDs have been known to cause bronchospasm in such patients.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Aceclofenac was not considered to have any mutagenic activity in three in vitro studies and an in vivo study in the mouse.

Aceclofenac was not found to be carcinogenic in either the mouse or rat.

Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some foetuses.

PREGNANCY AND LACTATION

Pregnancy: There is no information on the use of Aceclofenac during pregnancy. The regular use of NSAIDs during the last trimester of pregnancy may decrease uterine tone and contraction. NSAIDs use may also result in premature closure of the foetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the new born, delay onset and increase duration of labour.

Lactation: There is no information on the secretion of Aceclofenac to breast milk; there was however no notable transfer of radio-labelled (C^{14}) aceclofenac to the milk of lactating rats.

The use of Acedol should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus.

CHILDREN

There are no clinical data on the use of Aceclofenac in children and therefore it is not recommended for use in children

ELDERLY

The pharmacokinetics of Aceclofenac is not altered in elderly patients, therefore it is not considered necessary to modify the dose or dose frequency.

As with other non-steroidal anti-inflammatory drugs (NSAIDs), caution should be exercised in the treatment of elderly patients, who are generally more prone to adverse reactions, and who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication. The elderly should be monitored for GI bleeding for 4 weeks following initiation of NSAID therapy

ADVERSE EFFECTS

The majority of adverse reactions reported had been reversible and of a minor nature. The most frequent were gastro-intestinal disorders, in particular dyspepsia, abdominal pain, nausea and diarrhoea, and occasional occurrence of dizziness. Dermatological complaints including pruritus and rash and abnormal hepatic enzyme and serum creatinine levels had also been reported with the frequencies indicated in the following table.

If serious adverse reactions occur, Aceclofenac should be withdrawn.

The following is a table of adverse reactions reported during clinical studies with Aceclofenac.

WHO System Organ Class	Common 1 to 10%	Uncommon 0.1 to 1%	Rare or very rare < 0.1 %
Gastrointestinal System disorders	Dyspepsia, Abdominal pain, Nausea, Diarrhoea	Flatulence, Gastritis, Constipation, Vomiting, Ulcerative stomatitis	Melaena, Stomatitis, Haematemesis, Gastrointestinal haemorrhage, Gastric ulcer, Pancreatitis,
Urinary system disorders	-	-	Renal failure, Nephrotic syndrome
Central and peripheral nervous system disorders	Dizziness	Vertigo	Paraesthesia, Tremor
Psychiatric disorders	-	-	Depression, Abnormal dreaming, Somnolence, Insomnia.
Disorders of the skin and appendages	-	Pruritus Rash Eeczema Dermatitis Urticaria	Bullous dermatoses
Liver and Biliary Disorders	Hepatic enzymes increased	-	Hepatitis, Jaundice
Metabolic disorders	-	BUN increased Blood creatinine increased	Alkaline phosphatase increased, Hyperkalaemia
Cardiovascular disorders	-	-	Oedema in lower limbs, Palpitation, Cramps in legs, Flushing, Purpura
Respiratory disorders	-	-	Dyspnoea, Stridor, Bronchospasm
Haematological disorders	-	-	Anemia, Granulocytopenia, Thrombocytopenia, Neutropenia, Haemolytic anaemia
Body as a whole - general disorders	-	-	Allergic reaction, Anaphylactic reactions (including shock), Headache, Fatigue, Face oedema, Hot flushes, Weight increase
Others	-	-	Abnormal vision, Abnormal taste

Other rare or very rare class-effects reported with NSAIDs in general are:

Gastrointestinal System – Duodenal ulcer, Gastro-intestinal perforation

Urinary System – Interstitial nephritis

Central and Peripheral Nervous System – Optic neuritis

Psychiatric – Hallucination, Drowsiness, Confusion

Skin and Appendages – Epidermal necrolysis, Erythema multiforme, Exfoliative dermatitis

Respiratory – Aggravated asthma

Haematological – Aplastic anaemia

Others – Tinnitus, Photosensitivity, Malaise

OVERDOSAGE

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures.

There are no human data available on the consequences of Aceclofenac overdosage. The therapeutic measures to be taken are: absorption should be prevented as soon as possible after overdosage by means of gastric lavage and treatment with activated charcoal; supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

DOSAGE

Acedol is given twice a day by mouth; one tablet in the morning and one in the evening.

EXPIRY DATE

Do not use after the date of expiry.

STORAGE

Store below 30°C, Protected from moisture

PRESENTATION

Acedol is available in blister strip of 10 tablets.

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Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Baddi-173 205, Dist. Solan (H.P.), INDIA.