

APO-DICLO EC

Diclofenac sodium 25mg and 50mg tablets

Presentation

APO-DICLO EC 25mg tablets are yellow, round, biconvex tablets, 6.5mm in diameter, with an enteric coating identified 25 on one side. Each tablet contains 25mg diclofenac sodium and typically weighs 112mg.

APO-DICLO EC 50mg tablets are light brown, round biconvex tablets, 8.0mm in diameter, with an enteric coating identified 50 on one side. Each tablet contains 50mg diclofenac Sodium and typically weighs 225mg.

Uses

Actions

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) which exhibits anti-inflammatory, anti-rheumatic, analgesic and antipyretic activity. Its exact mode of action is not known but many of its actions appear to be associated with prostaglandins inhibition. Prostaglandins play a major role in the mediation of pain, inflammation and fever. Additional inhibitory effects on the formation and migration of other mediators of inflammation have also been proposed.

When used for symptomatic treatment, diclofenac sodium relieves pain and stiffness, reduces swelling and tenderness and in rheumatic diseases can improve grip strength and mobility.

When used for the relief of primary dysmenorrhoea, diclofenac sodium relieves the pain and reduces the extent of the bleeding.

Pharmacokinetics

When diclofenac sodium is administered as an enteric-coated tablet it is completely absorbed after passage through the stomach although onset of absorption may be delayed due to the tablet coating. Peak plasma concentrations (1.5 µg/mL) generally occur within 2 to 3 hours after ingestion of one 50mg tablet on an empty stomach. The presence of food delays absorption. After repeated administration pharmacokinetic behaviour does not alter. Provided the recommended dosage intervals are followed no accumulation occurs.

Diclofenac undergoes first-pass metabolism so that only 50-60% of a dose reaches the circulation and binding to plasma proteins is extensive (99.7%). The total apparent volume of distribution (Vd) is 0.12 to 0.17 L/kg and for central compartment Vd=0.04 L/kg.

Peak levels of diclofenac occur in the synovial fluid 2-4 hours after peak plasma concentrations have been reached but there is considerable inter-individual variation in the concentrations achieved with a given dose. Elimination from synovial fluid is less rapid (3 to 6 hours) than from plasma (1.5 to 2 hours). Diclofenac and its metabolites cross the placenta and small amounts distribute into breast milk.

Diclofenac is rapidly and extensively metabolised in the liver either by hydroxylation to phenolic metabolites with subsequent conjugation or by direct glucuronidation of the unchanged drug. Known phenolic metabolites are 3'-hydroxy-, 4'-hydroxy-, 5'-hydroxy-, 4',5'-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac. Two of these metabolites are biologically active although to a much smaller extent than diclofenac with 4'-hydroxydiclofenac having 3% of the anti-inflammatory potency of diclofenac. Four of the metabolites including the active ones have short plasma half-lives of 1-3 hours although the virtually inactive 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life.

Approximately 60% of a dose is excreted in urine as either glucuronide conjugates or the metabolites. Less than 1% is excreted in the urine as free diclofenac. The balance of the dose is excreted in faeces within 96 hours.

Use in renal or chronic hepatic impairment: Dosage adjustments may need to be made when dysfunction is severe.

Indications

Diclofenac is used for the relief of moderate pain and inflammation in:

1. Rheumatic disorders: e.g. ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile rheumatoid arthritis, painful syndromes of the vertebral column, non-articular rheumatism.
2. Acute attacks of gout.
3. Painful post-operative inflammation and swelling (including dental and orthopaedic procedures).
4. Painful or inflammatory gynaecological conditions e.g. primary dysmenorrhoea.
5. As an adjuvant in severe painful inflammatory infections of the ear, nose or throat.
6. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Diclofenac provides symptomatic relief but has not been shown to halt or reverse the underlying disease process. Fever alone is not an indication.

Dosage and Administration

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest duration should be used.

Adults:

For moderate to severe acute pain: Daily doses of 100 mg to 150 mg in 2 to 3 divided doses

For mild to moderate acute pain or long term chronic pain relief: Divided doses up to 75 mg or 100 mg daily. Maximum daily dose is 150 mg/day.

Primary Dysmenorrhoea: The daily dosage should be individually adjusted and is generally 50-150mg. An initial dose of 50-100mg should be given increasing as necessary over several menstrual cycles up to a maximum of 200mg/day. Treatment should be started on the first appearance of symptoms and continued for a few days as determined by the symptomatology.

Tablets should be swallowed whole with liquid before meals.

If a fast onset of action is required e.g. sprains, strains and post-operative inflammation, the tablets can initially be taken 30 minutes before food.

If long-term therapy is anticipated or the patient has a history of gastro-intestinal ulceration, it is advisable to take tablets with or after food to lessen the risk of duodenal ulceration.

Children:

Children aged 1 year or over: 0.5 to 2mg/kg bodyweight daily in divided doses. For juvenile rheumatoid arthritis the dosage may be increased up to a maximum of 3mg/kg, in divided doses.

APO-DICLO EC 50mg tablets are not recommended for use in children.

Elderly:

Dosage should be minimised and close monitoring is recommended.

Use in Impaired Renal Function:

Dosage reductions may be necessary when creatinine clearance is <10mL/min. In all cases of renal dysfunction, frequent monitoring is required.

Contraindications

Gastric or intestinal ulcer.

Known hypersensitivity to any component of the tablet.

Hypersensitivity to aspirin or other NSAIDs.

Patients with haemorrhagic diathesis.

Patients in who attacks of asthma, urticaria or active rhinitis are precipitated by acetylsalicylic acid or other agents, which inhibit prostaglandin-synthetase activity.

Warnings and Precautions

Asthmatics: bronchospasm has been reported with the use of NSAIDs.

Due to the importance of prostaglandins in maintaining renal blood flow, caution is required in patients with impaired cardiac or renal function, the elderly, patients being treated with diuretics and patients with substantial extracellular volume depletion.

Diclofenac can cause retention of salt and water leading to oedema. Serum electrolytes should be monitored periodically during long term therapy.

Diclofenac should be used with caution in patients suffering from liver dysfunction.

Platelet aggregation may be inhibited temporarily. Patients with haemostasis defects should be carefully monitored.

Porphyria: Use of diclofenac should be avoided in patients with hepatic porphyria as it may trigger an attack.

Elevation of liver enzymes: Initial elevations are reversible. However, if they persist or worsen during prolonged therapy, diclofenac should be discontinued.

Allergic reactions: including anaphylaxis have occasionally been reported on first exposure to diclofenac.

Coumarin anticoagulants: (see Drug Interactions).

Prolonged treatment: Periodic blood counts are recommended.

Cardiovascular Thrombotic Events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see Dosage and Administration).

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore caution is advised in patients with fluid retention or heart failure.

Gastrointestinal Events

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation, which may increase with dose or duration of use but can, occur at any time without warning. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur approximately 1% of patients treated for 3-6 months and in about 2-4% patents 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.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Severe Skin Reactions

NSAIDs may rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any sign of hypersensitivity.

Mutagenicity, Carcinogenicity and Teratogenicity

Studies of use of diclofenac in rats did not show any effect on the fertility of adult rats nor in the pre-, peri- and postnatal development of their offspring. No teratogenic effects were detected in mice, rats or rabbits. No mutagenic effects were observed in in vitro or in vivo experiments. No carcinogenic potential was detected in long term studies in rats and mice.

Use during Pregnancy

Category C.

Diclofenac should be avoided in pregnancy unless the benefits outweigh the potential risk to the foetus. This applies particularly to the last 3 months of pregnancy when in common with other prostaglandin synthetase inhibitors, diclofenac may cause closure of the foetal ducts arterioles, foetal renal impairment, inhibition of platelet aggregation and delay labour and birth.

Use in nursing mothers

Diclofenac is detected in breast milk following doses of 50 mg every 8 hours, but amounts are so small that no undesirable effects on the baby are likely.

Effects on ability to drive or use machinery

Diclofenac may cause some patients to become dizzy, light-headed or less alert. Patients should be aware of their reaction to Diclofenac before driving or using machinery.

Adverse Effects

Gastrointestinal, dermatological and central nervous system adverse effects are the most common seen. Most diclofenac-induced adverse effects occur during the first 3 to 6 months of treatment and are usually mild and transient.

Gastrointestinal effects:

May require discontinuation of diclofenac in a small number of patients.

Common: (>1%) Epigastric or abdominal discomfort, pressure, heaviness or distension; epigastric, gastric or abdominal pain; nausea; anorexia; diarrhoea, vomiting, flatulence, constipation or eructation.

Infrequent: (0.1-1%) Gastric and duodenal ulcerations and bleeding

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Rare: (<0.1%) Hyperacidity, stomatitis, coated tongue, peptic ulcer with perforation, lower gut disorders e.g. non-specific haemorrhagic colitis, exacerbation of ulcerative colitis and Crohn's disease; oesophageal lesions.

Central Nervous System:

Common: (>1%) Dizziness, headache, vertigo, malaise, insomnia, drowsiness, impaired concentration, impaired vision.

Rare: (<0.1%) Irritability, sweating, tiredness, sensory disturbances, tinnitus, convulsions, memory disturbances, disorientation, depression, anxiety, psychosis, tremor and taste disorders.

Dermatological reactions:

Common: (>1%) Rash, pruritus

Infrequent: (0.1-1.0%) Skin eruption, urticaria, erythema

Rarely: (<0.1%) alopecia, photosensitivity, bullous eruption, purpura, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, eczema and exfoliate dermatitis.

Renal:

Common: (>1%) Fluid and water retention; oedema with or without weight gain

Rare: (<0.1%) Haematuria, proteinuria, interstitial nephritis, papillary necrosis, nephrotic syndrome, acute renal failure.

Hepatic:

Common: (>1%) Elevation of transaminase enzymes (AST and ALT) which is usually transient.

Infrequent: (0.1-1%) Hepatitis with or without jaundice

Rare: (<0.1%) Fulminant hepatitis.

Haematological:

Rare: (<0.1%) Anaemia in some patients, secondary to GI bleeding; decreased platelet aggregation; leucopenia; thrombocytopenia; haemolytic anaemia; aplastic anaemia; agranulocytosis.

Hypersensitivity Reactions:

Infrequent: (0.1-1%) Bronchospasm or asthma; anaphylactic reactions, hypotension.

Rare: (<0.1%) Vasculitis, pneumonia

Cardiovascular:

Common: (>1%) Palpitations, angina, arrhythmias

Rare: (<0.1%) Exacerbation of cardiac failure

Interactions

Antihypertensive Agents: Diclofenac can reduce the antihypertensive effects of propranolol and other β -blockers as well as other antihypertensive agents.

Coumarin anticoagulants: There have been isolated reports of an increased risk of haemorrhage with the combination of warfarin and NSAIDs. Although the risk is reported to be low for diclofenac, careful monitoring of the INR or Prothrombin Time is required because diclofenac may cause GI bleeding and can inhibit platelet aggregation.

Diuretics: NSAIDs may reduce the activity of diuretics.

Potassium-sparing diuretics: concurrent administration with diclofenac has resulted in elevations of serum potassium levels; careful monitoring is advised.

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Digoxin, lithium and cyclosporin: Diclofenac may cause increased concentrations of these agents, with the potential for adverse side effects or toxicity. Frequent monitoring is necessary, especially in those with renal impairment.

Hypoglycaemic agents: Studies indicate that diclofenac does not potentiate the effects of oral hypoglycaemic. However, there have been isolated reports of both hypoglycaemia and hyperglycaemia.

Methotrexate: The combination of diclofenac and methotrexate has resulted in serious methotrexate toxicity which has sometimes been fatal. The risk is greatest if patients are taking high (anti-neoplastic) doses of methotrexate or if they have renal impairment. Caution is needed when diclofenac is administered 24 hours before or after treatment with methotrexate.

NSAIDs: Concomitant administration of systemic NSAIDs may increase the frequency of adverse effects.

Quinolones: Isolated reports suggest that quinolones (e.g. ciprofloxacin, norfloxacin) and NSAIDs could increase the risk of seizures. Although a causal relationship is still uncertain, caution is recommended.

Laboratory Tests: Diclofenac increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen or factors V and VII to XII. Statistically significant changes in thrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances and are unlikely to be clinically important.

Persistent abnormal or worsening renal, hepatic or haematological test results should be followed up carefully since they may be related to therapy.

Overdosage

There is no typical clinical picture resulting from an overdosage with diclofenac.

Management consists of supportive and symptomatic measures. Absorption should be prevented by inducing emesis or by gastric lavage, followed by administration of activated charcoal. Supportive and symptomatic treatment should be given if there are signs of hypotension, renal failure, convulsions, GI bleeding and respiratory depression.

Therapies such as forced diuresis, dialysis or haemoperfusion are likely to be ineffective.

Pharmaceutical Precautions

Shelf life 36 months from date of manufacture

Store below 30°C

Protect from heat, light and moisture.

Medicine Classification

Prescription-Only medicine.

Pharmacist-Only Medicine for 25mg when sold in packs containing 30 or less tablets.

Package Quantities

APO-DICLO EC 25mg tablets:

Bottles of 30 and 100 tablets.

Blister packs of 30 and 90 tablets

APO-DICLO EC 50mg tablets:

Bottles of 100 and 500 tablets.

Blister packs of 30 and 90 tablets.



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Further Information

Contains Dextrates.

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Date of Preparation

20 June 2007