

PACKAGE INSERT TEMPLATE FOR DICLOFENAC SODIUM ENTERIC COATED TABLET

Brand or Product Name

[Product name] Enteric Coated Tablet 25mg

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Name and Strength of Active Substance(s)

Diclofenac sodium 25mg

Diclofenac sodium 50mg

Product Description

[Visual description of the appearance of the product (eg colour, markings etc)

eg :Tablet - White, circular flat beveled edge enteric-coated tablets marked '100' on one side]

Pharmacodynamics

Mechanism of action

Diclofenac sodium is a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain and fever. Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

Pharmacodynamic effects

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac sodium elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

In post-traumatic and post-operative inflammatory conditions, diclofenac sodium relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema. Diclofenac sodium has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. In primary dysmenorrhoea, diclofenac sodium is capable of relieving the pain and reducing the extent of bleeding.

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Pharmacokinetics

Absorption

Diclofenac is completely absorbed from the gastro-resistant tablets after their passage through the stomach. Although absorption is rapid, its onset may be delayed due to the gastro-resistant coating of the tablet. Mean peak plasma concentrations of 1.5 micrograms/mL (5 micromol/L) are attained on average 2 hours after ingestion of one tablet of 50 mg. The amount absorbed is linearly related to the size of the dose.

The passage of a tablet through the stomach is slower when ingested with or after a meal than when it is taken before a meal, but the amount of diclofenac absorbed remains the same. Since about half of diclofenac is metabolised during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) following oral or rectal administration is about half that following an equivalent parenteral dose.

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed. The plasma concentrations attained in children given equivalent doses (mg/kg body weight) are similar to those obtained in adults.

Distribution

99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 L/kg. Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma values, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

Biotransformation

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-,4'-hydroxy-,5-hydroxy-,4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac.

Elimination

Total systemic clearance of diclofenac from plasma is 263 ± 56 mL/min (mean value \pm SD). The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive.

About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates.

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Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Characteristics in patients

No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed. In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile. In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

Indication

Treatment of:

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
- Acute attacks of gout.
- Painful post-traumatic and post-operative inflammation and swelling.
- Primary dysmenorrhoea.

Recommended Dosage

As a general recommendation, the dose should be individually adjusted and the lowest effective dose given for the shortest possible duration.

The tablets should be swallowed whole with liquid, preferably before meals, and must not be divided or chewed.

Adults

The recommended initial daily dose is 100 to 150 mg. In milder cases, as well as for long term therapy, 75 to 100 mg daily is usually sufficient.

The total daily dose should generally be divided into 2 to 3 doses. To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of a suppository at bedtime (up to a total maximum daily dose of 150 mg).

In primary dysmenorrhoea, the daily dose should be individually adjusted and is generally 50 to 150 mg. A dose of 50 to 100 mg should be given initially and, if necessary, increased over the course of several menstrual cycles up to a maximum of 200 mg/day. Treatment should be started

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on appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

Children and adolescents

Children aged 1 year or over and adolescents should be given 0.5 to 2 mg/kg body weight daily in 2 to 3 divided doses, depending on the severity of the disorder. For treatment of juvenile rheumatoid arthritis, the daily dose can be raised up to a maximum of 3 mg/kg daily, given in divided doses. The maximum daily dose of 150 mg should not be exceeded.

Because of their dosage strength, Diclofenac Sodium Enteric Coated Tablet 50mg are not recommended for use in children and adolescents below 14 years of age; Diclofenac Sodium Enteric Coated Tablet 25mg could be used in these patients.

Mode of Administration

Oral

Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation.
- Last trimester of pregnancy
- Severe hepatic, renal or cardiac failure
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac sodium is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

Warnings and Precautions

[Specific package insert requirement for diclofenac sodium]

PRECAUTION:

Severe cutaneous reactions, including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for signs of hypersensitivity reactions. Discontinue diclofenac sodium immediately if rash occurs.

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[Specific package insert requirement for NSAID]

WARNING

RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.

Like other NSAIDs, diclofenac sodium may mask the signs and symptoms of infection due to its pharmacodynamic properties.

The concomitant use of diclofenac sodium with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

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Gastrointestinal effects

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors.

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated.

Hepatic effects

Close medical surveillance is required when prescribing diclofenac sodium to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac sodium, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac sodium should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using diclofenac sodium in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using diclofenac sodium in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

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Haematological effects

During prolonged treatment with diclofenac sodium, as with other NSAIDs, monitoring of the blood count is recommended. Like other NSAIDs, diclofenac sodium may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac sodium should refrain from driving or using machines.

Interactions with Other Medicaments

The following interactions include those observed with diclofenac sodium enteric-coated tablets and/or other pharmaceutical forms of diclofenac.

Lithium

If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin

If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents

Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Other NSAIDs and corticosteroids

Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects.

Anticoagulants and anti-platelet agents

Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients

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receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs)

Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding.

Antidiabetics

Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate

Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

Ciclosporin

Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Quinolone antibacterials

There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

Potent CYP2C9 inhibitors

Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

Phenytoin

When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Statement on Usage During Pregnancy and Lactation

Pregnancy

The use of diclofenac in pregnant women has not been studied. Therefore, diclofenac sodium should not be used during the first two trimesters of pregnancy unless the potential benefit to the

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mother outweighs the risk to the foetus. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus. Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/foetal development, parturition or postnatal development.

Lactation

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac sodium should not be administered during breast feeding in order to avoid undesirable effects in the infant.

Fertility

As with other NSAIDs, the use of diclofenac sodium 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 diclofenac sodium should be considered.

Adverse Effects / Undesirable Effects

[Specific package insert requirement for diclofenac sodium]

Adverse effects:

Dermatological: Occasional - rashes or skin eruptions.

Cases of hair loss, bullous eruptions, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and photosensitivity reactions have been reported.

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac sodium, should refrain from driving or using machines.

The following undesirable effects include those reported with diclofenac sodium enteric coated tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.

Immune system disorders

Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).

Very rare: Angioneurotic oedema (including face oedema).

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Psychiatric disorders

Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders

Common: Headache, dizziness.

Rare: Somnolence.

Very rare: Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

Eye disorders

Very rare: Visual disturbance, vision blurred, diplopia.

Ear and labyrinth disorders

Common: Vertigo.

Very rare: Tinnitus, hearing impaired.

Cardiac disorders

Very rare: Palpitations, chest pain, cardiac failure, myocardial infarction.

Vascular disorders

Very rare: Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders

Rare: Asthma (including dyspnoea).

Very rare: Pneumonitis.

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.

Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation).

Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.

Hepatobiliary disorders

Common: Transaminases increased.

Rare: Hepatitis, jaundice, liver disorder.

Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure

Skin and subcutaneous tissue disorders

Common: Rash.

Rare: Urticaria.

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Very rare: Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.

Renal and urinary disorders

Very rare: Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.

General disorders and administration site conditions

Rare: Oedema.

Overdose and Treatment

Symptoms

There is no typical clinical picture resulting from diclofenac overdose. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures

Management of acute poisoning with NSAIDs, including diclofenac essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism. Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

Storage Conditions

Store below°C

Dosage Forms and Packaging Available

[Packaging type & pack size eg

Tablet - Alu-alu blister of 10s X 10/box, HDPE bottle of 30s/box]

Name and Address of Manufacturer

[Name & full address of manufacturer]

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Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]