

hovid CLOFENAC-50 Suppositories

DESCRIPTION

White to yellowish, torpedo-shaped suppository

COMPOSITION

Each suppository contains diclofenac sodium 50 mg.

ACTIONS AND PHARMACOLOGY

Diclofenac sodium is a nonsteroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase).

PHARMACOKINETICS

Absorption: Absorption is rapid; although the rate of absorption is slower than from enteric-coated tablets administered orally. After the administration of 50 mg suppositories, peak plasma concentrations are attained on average within 1 hour, but maximum concentrations per dose unit are about two thirds of those reached after administration of enteric-coated tablets.

Bioavailability: The AUC is approximately a half of the value obtained from a parenteral dose.

Accumulation does not occur, provided the recommended dosage intervals are observed.

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

Metabolism: 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, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination: The total systemic clearance of diclofenac in plasma is 263 ± 56 mL/min (mean value $\pm$ SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours.

About 60% of the administered dose is excreted in the urine in the form of the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

INDICATION

Adults and Elderly: Relief of all grades of pain and inflammation in a wide range of conditions, including:

- arthritis conditions: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout,
- acute musculo-skeletal disorders such as periartthritis (for example frozen shoulder), tendinitis, tenosynovitis, bursitis,
- other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.

hovid Clofenac-50 Suppositories are not indicated for use in children.

CONTRAINDICATIONS

- Hypersensitivity to diclofenac sodium or any of the excipients.
- Active, gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Last trimester of pregnancy.
- Severe hepatic, renal or cardiac failure.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.
- Proctitis
- Severe cardiac failure (see section WARNINGS AND PRECAUTIONS) such as established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

WARNINGS AND PRECAUTIONS

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms, especially for use in frail elderly patients or those with a low body weight.

- The concomitant use of diclofenac sodium with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

- As with other nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/ anaphylactoid reactions, can also occur without earlier exposure to the drug.

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

- Gastrointestinal effects:** Gastro-intestinal bleeding (haematemesis, melaena) ulceration or perforation which can be fatal has been reported with all NSAIDs including diclofenac and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the drug should be withdrawn.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastro-intestinal disorders, or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation.

To reduce the risk of GI toxicity, the treatment should be initiated and maintained at the lowest effective dose. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin) or medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly when 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 such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid.

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

- Hepatic effects:** Close medical surveillance is required when prescribing diclofenac sodium to patients with impairment of 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, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), diclofenac sodium should be discontinued.

Hepatitis may occur with diclofenac without prodromal symptoms. Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

- Renal effects:** As fluid retention and oedema have been reported in association with NSAIDs 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 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 in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state.

- Skin effects:** 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.

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.

- 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.

- Cardiovascular and cerebrovascular effects:** Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

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, including diclofenac.

Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, maybe associated with an increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke).

Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤ 100 mg daily when treatment continues for more than 4 weeks.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

- Hematological effects:** During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Diclofenac sodium may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

- 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.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

- Female fertility:** The use of diclofenac sodium may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac sodium should be considered.

- Effects on ability to drive and use machines:** Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness or fatigue while taking NSAIDs should refrain from driving or operating machinery.

PREGNANCY AND LACTATION

Pregnancy: Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. There is an increased risk of miscarriage and or 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.

If diclofenac sodium is used by a woman attempting to conceive, or during the 1st 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-hydramnios. 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, diclofenac sodium is contraindicated during the third trimester of pregnancy.

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

DRUG INTERACTIONS

Lithium or Digoxin: If used concomitantly, diclofenac sodium may increase plasma concentrations of lithium or digoxin. Monitoring of the serum lithium level or serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac sodium with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

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 periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Anticoagulants and anti-platelet agents: Since concomitant administration could increase the risk of bleeding, caution and close monitoring of the patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of SSRIs may increase the risk of gastrointestinal bleeding.

Antidiabetics: Monitoring of the blood glucose level is recommended during concomitant therapy.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before 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 given in patients not receiving ciclosporin.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostaglandin effects of both NSAID and calcineurin inhibitor.

Quinolone antibacterials: 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 an NSAID.

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

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/cholestyramine.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

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

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

MAIN SIDE/ ADVERSE EFFECTS

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention: very common: (>1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1000); very rare (<1/10,000); not known: cannot be estimated from available data.

The following undesirable effects include those reported with other short-term or long-term use.

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, leucopenia, 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).

Psychiatric disorders

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

Nervous system disorders

Common: Headache, dizziness; **Rare:** Somnolence, tiredness

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

Unknown: Confusion, hallucinations, disturbances of sensation, malaise.

Eye disorders

Very rare: Visual disturbance, vision blurred, diplopia

Unknown: Optic neuritis

Ear and labyrinth disorders

Common: Vertigo.

Very rare: Tinnitus, hearing impaired

Cardiac disorders

Uncommon: Myocardial infarction, cardiac failure, palpitations, chest pain.

(*The frequency reflects data from long-term treatment with a high dose, 150 mg/day.)

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

Vascular disorders

Very rare: Hypertension, hypotension, 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 (sometimes fatal particularly in the elderly).

Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative 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.

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.

hovid CLOFENAC-50 Suppositories**General disorders and administration site conditions**

Rare: Application site irritation, oedema

Reproductive system and breast disorders

Very rare: Impotence

Description of selected adverse drug reaction

Arteriothrombotic events: Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment (see section WARNINGS AND PRECAUTIONS).

OVERDOSE AND TREATMENT

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible.

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 potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patients clinical condition.

DOSAGE AND ADMINISTRATION

As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section WARNINGS AND PRECAUTIONS).

Not to be taken by mouth, as per rectal administration only.

The suppositories should be inserted well into the rectum. It is recommended to insert the suppositories after passing stools.

Adults: 75-150 mg daily, in divided doses. The recommended maximum daily dose is 150 mg. This may be administered using a combination of dosage forms, e.g. tablets and suppositories.

Elderly: Although the pharmacokinetics of diclofenac sodium are not impaired to any clinically relevant extent in elderly patients, nonsteroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight and the patient should be monitored for GI bleeding during NSAID therapy.

Hepatic and renal impairment:

Diclofenac is contraindicated in patients with severe hepatic and renal impairment. Caution is advised when administering diclofenac to patients with mild to moderate hepatic and renal impairment.

Established cardiovascular disease or significant cardiovascular risk factors:

Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤ 100 mg daily if treated for more than 4 weeks (see section WARNINGS AND PRECAUTIONS).

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage: Store below 30°C. Protect from light and moisture.

Presentation/Packing: Blister of 2 x 5's

Product Registration Holder/Repacked by: **HIVID Bhd.**

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Manufactured by: Jiangsu Farever Pharmaceutical Co., Ltd. No. 18, Yangshan Road Street Avenue, Economy Development Zone, Xuzhou City, P. R. China.

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