

Directions for Use

Please Read Carefully!

Diclac Retard 100mg Tablet

COMPOSITION

One modified-release tablet contains 100mg diclofenac sodium; lactose monohydrate; methylhydroxypropylcellulose; magnesium stearate.

PRODUCT DESCRIPTION

White, round and biconvex tablets.

PHARMACODYNAMICS

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances.

ATC code: M01AB05

Mechanism of action (MoA)

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 to be fundamental to its mechanism of action. Prostaglandins play an important role in causing inflammation, pain and fever.

Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans.

Pharmacodynamics (PD)

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac 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 rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

Diclofenac also has beneficial effects on the symptoms of migraine attacks.

PHARMACOKINETICS

Absorption

Judged by urinary recovery of unchanged diclofenac and its hydroxylated metabolites, the same amount of diclofenac is released and absorbed from diclofenac prolonged-release tablets as from gastro-resistant tablets. However, the systemic availability of diclofenac from diclofenac prolonged-release tablets is on average about 82% of that achieved with the same dose of diclofenac administered in the form of gastro-resistant tablets (possibly due to release-rate dependent "first-pass" metabolism). As a result of a slower release of the active substance from diclofenac prolonged-release tablets, peak concentrations attained are

lower than those observed following the administration of gastro-resistant tablets.

Mean peak concentrations of 0.5 micrograms/mL or 0.4 micrograms/mL (1.6 or 1.25 micromol/L) are reached on average 4 hours after ingestion of a prolonged-release tablet of 100 mg or 75 mg.

Food has no clinically relevant influence on the absorption and systemic availability of diclofenac prolonged-release tablets.

On the other hand, mean plasma concentrations of 13 ng/mL (40 nmol/L) can be recorded at 24 hours (16 hours) after administration of diclofenac prolonged-release tablets 100 mg (75 mg).

Since about half of diclofenac is metabolized 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.

Trough concentrations are around 22 ng/mL or 25 ng/mL (70 nmol/L or 80 nmol/L) during treatment with diclofenac prolonged-release tablets 100 mg once daily or 75 mg twice daily.

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distribution

99.7% of diclofenac binds 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 reached. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma levels, 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.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

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

Linearity/non-linearity

The amount absorbed is linearly related to the dose strength.

Special populations

Geriatric patients

No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed. However, in a few elderly patients a 15-minute intravenous infusion resulted in 50% higher plasma concentrations than expected from the data on young healthy subjects.

Renal impairment

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 less than 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.

Hepatic impairment

In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

A random, cross-over study was carried out in 12 healthy volunteers. A single dose of **Diclac® retard 100mg Tab** or Voltaren Retard Geigy (containing 100mg retard tablet of diclofenac sodium) by CIBA-CEIGY Italy was administered to the subjects and the plasma concentrations of diclofenac determined at various time points over 12 hours.

Results of this study showed that plasma level of diclofenac after **Diclac® retard 100mg Tab** were comparable to plasma levels after Voltaren Retard tablets. Thus, **Diclac® retard 100mg Tab** is bioequivalent to Voltaren Retard. (Ref: Bioavailability studies of the product 'AG 109' by Gechim s.r.l.-MILANO, Italy)

INDICATIONS

Treatment of:

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

RECOMMENDED DOSE

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).

Dosage for adults:

Depending on the severity of the illness, the recommended daily dose ranges between 50 and 150mg of diclofenac sodium. Adults: receive 1 modified-released tablet **Diclac® retard 100mg Tab** per day.

If required, the daily dose can be increased to 150mg active ingredient with additional administration of

one enteric-coated tablet containing 50mg diclofenac sodium.

Dosage for children and adolescents:

Diclac® retard 100mg Tab is not appropriate for children and adolescents due to its high content of active ingredient

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 $\leq 100\text{mg}$ daily if treated for more than 4 weeks (see section WARNINGS AND PRECAUTIONS)

ROUTE OF ADMINISTRATION

Oral

The tablet should be swallowed whole together with a sufficient quantity of liquid. The duration of treatment is to be determined by the physician.

CONTRAINDICATIONS

Diclac® retard 100mg Tab may not be administered in the following cases:

- Known hypersensitivity to the active substance or to any of the other excipients
- Active gastric or intestinal ulcer, bleeding or perforation (see section WARNING AND PRECAUTIONS and SIDE EFFECTS)
- Last trimester of pregnancy (see section PREGNANCY AND LACTATION)
- Children and adolescents
- Hepatic failure
- Renal failure ($\text{GFR} < 15\text{mL/min/1.73m}^2$)
- Severe cardiac failure (see section WARNINGS AND PRECAUTIONS)
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom the use of acetylsalicylic acid or other NSAIDs can precipitate asthma, angioedema, urticaria or acute rhinitis (i.e. NSAID-induced cross-reactivity reactions) (see section WARNINGS AND PRECAUTIONS and SIDE EFFECTS).

Diclac® retard 100mg Tab should only be administered after making the strictest assessment of the benefit/risk relationship in the following cases:

- inducible porphyria,
- in the first and second trimester of pregnancy,
- during the lactation period.

Especially careful medical monitoring is necessary for:

- patients with gastrointestinal complaints or with signs of gastric or intestinal inflammations or intestinal ulcers (ulcerative colitis, Crohn's disease) in the anamnesis,
- patients directly after larger operations,
- elderly patients.

Diclac® retard may only be administered to patients who experienced hypersensitivity reactions (e.g. asthmatic attacks, skin reactions or acute allergic rhinitis) to an earlier treatment with non-steroidal anti-inflammatory drugs or analgesics if specific precautionary measures are taken (i.e. emergency service must be provided). Patients with asthma, chronic bronchoconstrictive (obstructive) respiratory diseases, hay fever or swelling of nasal mucosa (so-called nasal polyps) react more frequently than other patients to non-steroidal antirheumatic drugs, experiencing asthmatic attacks, local swelling of the skin or mucosa (so-called Quincke's oedema) or hives (urticaria).

The sodium content of diclofenac sodium should be considered when selecting an NSAID for patients who must restrict their sodium intake.

WARNINGS AND PRECAUTIONS

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.

Gastrointestinal effects

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have 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 gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the treatment should be discontinued.

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 gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section SIDE EFFECTS). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly

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 low dose acetylsalicylic acid (ASA), or other drugs 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 (see section INTERACTIONS).

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

NSAIDs, including diclofenac, may be associated with increased risk of gastrointestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastrointestinal surgery.

Cardiovascular effects

Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, may be 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.

Hematologic effects

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

Respiratory effects (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 caution 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.

Hepatobiliary effects

Close medical surveillance is required when prescribing diclofenac 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 (e.g., in the form of tablets or suppositories), 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 should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

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

Skin reactions

Severe cutaneous reactions, including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), and generalised bullous fixed drug eruption 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.

Patients appear to be at highest risk of 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. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

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

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 of any cause, e.g., before or after major surgery (see section CONTRAINDICATIONS). Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Geriatric patients

Caution is indicated in the elderly on basic medical grounds, especially in frail elderly patients or those with a low body weight.

Interactions with NSAIDs

The concomitant use of diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to undesirable effects (see section INTERACTIONS).

Masking signs of infections

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

INTERACTIONS

The following interactions include those observed with diclofenac gastro-resistant tablets, prolonged-released tablets, suppositories, and/or other pharmaceutical forms of diclofenac.

Observed interactions to be considered

CYP2C9 inhibitors:

Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to 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 (see section WARNINGS AND PRECAUTIONS).

Ciclosporin and tacrolimus:

Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin and tacrolimus 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 or tacrolimus.

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 (see section WARNINGS AND PRECAUTIONS)

Quinolone antibacterials:

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

Anticipated interactions to be considered

Other NSAIDs and corticosteroids:

Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section WARNINGS AND PRECAUTIONS).

Anticoagulants and anti-platelet agents:

Caution is recommended since concomitant administration could increase the risk of bleeding (see section WARNINGS AND PRECAUTIONS). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of hemorrhage in patients 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 (see section WARNINGS AND PRECAUTIONS).

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 hypoglycemic and hyperglycemic 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.

There have also been isolated reports of metabolic acidosis when diclofenac was coadministered with metformin, especially in patients with pre-existing renal impairment.

Phenytoin:

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

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.

CYP2C9 inducers:

Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac.

PREGNANCY AND LACTATION**Pregnancy**

There are insufficient data on the use of diclofenac in pregnant women. Some epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy, however the overall data are inconclusive.

Diclofenac has been shown to cross the placental barrier in humans. Use of NSAIDs, including diclofenac, can cause uterine inertia, premature closure of the foetal ductus arteriosus and foetal renal impairment leading to oligohydramnios.

Because of these risks, diclofenac should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the foetus.

In addition, diclofenac should not be used during the third trimester of pregnancy (see sections CONTRAINDICATIONS).

Clinical considerations**Foetal Adverse Drug Reactions*****Premature Closure of Foetal Ductus Arteriosus***

As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of premature closure of the foetal ductus arteriosus (see sections CONTRAINDICATIONS).

Oligohydramnios/Foetal Renal Impairment

Risk of foetal renal impairment with subsequent oligohydramnios has been observed when NSAIDs

(including diclofenac) were used from the 20th week of pregnancy onwards.

If an NSAID is necessary from the 20th week gestation to the end of the 2nd trimester, limit the use to the lowest effective dose and shortest duration possible (see section 4 Dosage regimen and administration). If diclofenac treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue diclofenac and follow up according to clinical practice.

Labour or Delivery

There are no studies on the effects of diclofenac during labour or delivery. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia (see sections CONTRAINDICATIONS).

Lactation

Risk Summary

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

Female fertility

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

SIDE EFFECTS

Tabulated summary of adverse drug reactions Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

The following undesirable effects include those reported with diclofenac gastro-resistant tablets/prolonged-released tablets/ suppositories and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Table 1 –Adverse drug reactions

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: Angioedema (including face oedema)

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,

dysgeusia, cerebrovascular accident

Eye disorders

Very rare: Visual impairment, blurred vision, diplopia

Ear and labyrinth disorders

Common: Vertigo

Very rare: Tinnitus, impaired hearing

Cardiac disorders

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

Not known: Kounis syndrome

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, decreased appetite

Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, haemorrhagic diarrhoea, melena, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis, or perforation, which may lead to peritonitis)

Very rare: Colitis (including haemorrhagic colitis, ischemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, intestinal diaphragm disease, 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 multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction purpura, Henoch-Schonlein purpura, pruritus

Unknown: Fixed drug eruption, generalised bullous fixed drug eruption

Renal and urinary disorders

Very rare: Acute kidney injury (acute renal failure), haematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis

General disorders and administration site condition

Rare: Oedema

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

Description of selected adverse drug reactions

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 (150mg daily) and during long-term treatment (see section WARNINGS AND PRECAUTIONS)

Visual effects

Visual disturbances such as visual impairment, blurred vision or diplopia appear to be NSAID class effects and are usually reversible on discontinuation. A likely mechanism for the visual disturbances is the inhibition of prostaglandin synthesis and other related compounds that alter the regulation of retinal blood flow resulting in potential changes in vision. If such symptoms occur during diclofenac treatment, an ophthalmological examination may be considered to exclude other causes.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms

There is no typical clinical picture resulting from diclofenac overdose. Overdose 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 hemoperfusion 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous disturbances while taking diclofenac should refrain from driving a vehicle or operating machines. (see section SIDE EFFECTS).

STORAGE

Store in a cool dry place, below 30°C.

Keep out of reach of children

Jauhi daripada kanak-kanak.

PRESENTATIONS AND PACKAGE SIZES:

Boxes of 20, 50 and 100 modified-release tablets

Do not use this drug after the expiry date printed on the package.

MANUFACTURED FOR:

Hexal AG
Holzkirchen, Germany

by:

Salutas Pharma GmbH
(a subsidiary of Hexal AG)
Barleben, Germany.

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