

DICLAX SR

Diclofenac Sodium

Name of the Medicine

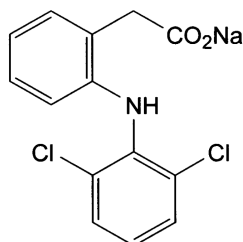
DICLAX SR

Diclofenac sodium 75 mg sustained-release tablet and 100 mg sustained-release tablet.

Description

Diclofenac sodium is an anti-inflammatory product. The chemical name is sodium 2-[(2,6-dichlorophenyl)amino]phenyl]acetate. It has a molecular formula and weight of $C_{14}H_{10}Cl_2NNaO_2$ and 318.1 respectively.

The structural formula is:



The tablets contain as excipients: magnesium stearate, hypromellose, titanium dioxide, diethyl phthalate, ethylcellulose, macrogol, ferric oxide (red), ferric oxide (yellow), povidone, stearic acid and purified talc.

Pharmacology

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances (ATC code: M01A B05).

Mechanism of action

DICLAX SR contains diclofenac sodium, 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 DICLAX SR 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, DICLAX SR rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

DICLAX SR 75 mg tablets are particularly suitable for patients in whom a daily dose of 75 mg or 100 mg is appropriate to the clinical picture. The possibility of prescribing the medicinal product in a single daily dose considerably simplifies the long-term treatment and helps to avoid the possibility of dosage errors. DICLAX SR 75 mg tablets also allow the maximum daily dose of 150 mg to be given in a balanced b.i.d schedule.

Pharmacokinetic properties

Absorption

Judged by urinary recovery of unchanged diclofenac and its hydroxylated metabolites, the same amount of diclofenac is released and absorbed from DICLAX SR tablets as from gastro-resistant tablets. However the systemic availability of diclofenac from DICLAX SR 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 DICLAX SR 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 micro mol/L) are reached on average 4 hours after ingestion of a SR tablet of 75 mg.

Food has no clinically relevant influence on the absorption and systemic availability of DICLAX SR 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 SR 100 mg (75 mg) tablet. The amount absorbed is linearly related to the dose strength.

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.

Trough concentrations are around 22 ng/mL or 25 ng/mL (70 nmol/L or 80 nmol/L) during treatment with DICLAX SR 100 mg once daily or 75 mg twice daily.

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 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.

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.

Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac had no influence on the fertility of parent animals in rats. The prenatal, perinatal and postnatal development of the offspring was not affected.

Indications

DICLAX SR is indicated for the 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
- Post-traumatic and post-operative pain, inflammation and swelling (eg: following dental or orthopaedic surgery)
- Painful and/or inflammatory conditions in gynaecology (eg: primary dysmenorrhoea or adnexitis)

Contraindications

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

Precautions

General

The concomitant use of DICLAX SR 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 adverse effects.

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 in approximately 1% of patients treated for 3-6 months and in about 2-4 patients 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.

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 that could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (SSRIs).

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 Adverse effects**).

Severe Skin Reactions

NSAIDs may very 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 other sign of hypersensitivity.

Hypersensitivity

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

Masking Infection

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

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (ie: 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/analgesic-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 (eg: with skin reactions, pruritus or urticaria).

Hepatic Function

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

As with other NSAIDs, values of one or more liver enzymes may increase. During prolonged treatment with DICLAX SR, 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 (eg: eosinophilia, rash), DICLAX SR should be discontinued. Hepatitis may occur without prodromal symptoms.

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

Renal Function

As fluid retention and oedema have been reported in association with NSAID therapy, 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 (eg: before or after major surgery). Monitoring of renal function is recommended as a precautionary measure when using DICLAX SR in such cases (**see Contraindications**). Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Haematological effects

During prolonged treatment with DICLAX SR, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, DICLAX SR may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

Use in the Elderly

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 of those with a low body weight.

Use in Pregnancy

The use of diclofenac in pregnant women has not been studied. Therefore, DICLAX SR should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweighs the risk to the foetus. As with other NSAIDs, use during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus (**see Contraindications**). Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/foetal development, parturition or postnatal development (**see Preclinical safety data**).

Use in Lactation

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

Fertility

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

Effects on Ability to Drive or Operate Machinery

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

Interactions

The following interactions include those observed with DICLAX SR and other pharmaceutical forms of diclofenac.

Lithium

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

Digoxin

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

Diuretics and antihypertensive agents

Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (eg; 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 (**see Precautions**).

Other NSAIDs and corticosteroids

Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal adverse effects (**see Precautions**).

Anticoagulants and anti-platelet agents

Caution is recommended since concomitant administration could increase the risk of bleeding (**see Precautions**). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs)

Concomitant administration of systemic NSAIDs and SSRIs may increase the risk of gastrointestinal bleeding (**see 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 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 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 may be increased.

Cyclosporin

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

Quinolone antibacterials

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

Adverse effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: common ($\geq 1/100$, $\geq 1/10$); uncommon ($\geq 1/1,000$, $\geq 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($\geq 1/10,000$), including isolated reports.

The following adverse effects include those reported with DICLAX SR gastro-resistant tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Table 1

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).

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.

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.

General disorders and administration site conditions

Rare: Oedema.

Dosage and Administration

This product is not able to deliver all approved dose regimes.

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

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

Adults

The recommended daily dose is 100–150 mg, in 1 or 2 divided doses. In milder cases, as well as for long-term therapy, 75-100 mg daily is usually sufficient.

Where the symptoms are more pronounced during the night or in the morning, DICLAX SR 75 mg tablets should preferably be taken in the evening.

Children and Adolescents

Because of their dosage strength, DICLAX SR 75 mg tablets are not suitable for children and adolescents.

Overdosage

Symptoms

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

Presentation and Storage conditions

DICLAX SR 75 mg: A pink, triangular film coated tablet.

DICLAX SR 100 mg: A light red, circular, biconvex, film coated tablet of approximately 9 mm diameter.

Storage

DICLAX SR 75 mg and 100 mg tablets in blisters should be stored below 30 °C, protected from light and moisture. DICLAX SR 75 mg and 100 mg tablets in bottles should be stored below 25 °C. The shelf life is 3 years.

Pack quantities

DICLAX SR 75 mg tablets: Blisters in cartons containing 30 tablets and bottles containing 500 tablets.

DICLAX SR 100 mg tablets: Blisters in cartons containing 30 tablets or 90 tablets and bottles containing 500 tablets.

Medicine Classification

Prescription Medicine.

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Date of Preparation

July 2007