

PRESCRIBING INFORMATION

Swiss Relief Dual Release, 75 mg capsules

1. NAME OF THE MEDICINAL PRODUCT

Swiss Relief Dual Release 75 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diclofenac sodium 75 mg (25 mg diclofenac sodium as gastro-resistant pellets and 50 mg diclofenac sodium as prolonged-release pellets).

3. PHARMACEUTICAL FORM

Capsules with modified release, hard.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

As a non-steroidal anti-inflammatory analgesic in symptomatic management of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, acute musculo-skeletal disorders such as peri-arthritis, tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations, relief of pain in fractures, low back pain, acute gout, psoriatic arthropathy.

In the management of pain and inflammation associated with orthopaedic, dental and minor surgery.

4.2 Posology and method of administration

The treatment should be started with the lowest presumed effective dose for the shortest duration necessary to control symptoms, possibly adjusted later.

Individual:

Adults: One capsule daily. Dose may be increased to two capsules daily if necessary. The first dose should be taken in the morning with breakfast and the second if required 8-12 hours later.

The maximum dose is 150 mg/24 hours.

The capsules must be swallowed whole with plenty of liquid. To be taken preferably with or after food.

Children: Not for use in children.

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Treatment management:

In the case of treatment for longer periods, laboratory values with respect to the blood picture and liver and kidney function should be monitored.

4.3 Contra-indications

Swiss Relief Dual Release Capsules is contra-indicated in patients with:

- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Inflammatory gastrointestinal disorders
- Hypersensitivity to diclofenac or one of the excipients
- Severe hepatic, renal and cardiac failure
- During the last trimester of pregnancy
- In conditions with an increased tendency to bleeding
- Owing to cross-reaction, the preparation must not be given to patients, especially asthmatics, in whom ingestion of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs provoke symptoms of asthma, angioedema, urticaria or rhinitis
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

4.4 Special warnings and special precautions for use

Patients with gastrointestinal disorders or a history of ulcer and patients with ulcerative colitis, Crohn's disease, SLE, and haemopoietic or coagulation disturbances should be closely monitored during treatment with diclofenac.

In all patients: There is a strong relation between the dose and serious gastrointestinal side effects. The lowest effective dose should therefore be the aim for each patient. This means that combinations with different NSAIDs, including cyclo-oxygenase-2 selective inhibitors, taken at the same time should be avoided.

Depending on the importance of the prostaglandins for maintaining the renal blood flow, particular caution is indicated when diclofenac is used in the presence of impaired heart, liver, or kidney function. This also applies to treatment with nephrotoxic agents, such as cyclosporin. In elderly patients, especially those receiving diuretics, and patients who lose large extracellular volumes, for instance in the peri- or post-operative phase of major surgical interventions, the risk of fluid retention and deterioration of kidney function must be taken into account.

Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Caution must be exercised in the treatment of elderly patients, who generally have a greater tendency towards side effects. The consequences of, for example, gastrointestinal bleeding and/or perforation are often more serious and may occur at any time during the treatment, with no warning signals and without having occurred earlier. Elderly patients are also more likely to suffer from impaired kidney, heart, or liver function.

Patients treated with oral anticoagulants or antidiabetic agents should be monitored with respect to overdosage, when Swiss Relief Dual Release Capsules is given concurrently. Laboratory tests should be carried out in order to check that the desired effect of anticoagulants is maintained. Various antiphlogistics may block the diuretic effect and potentiate the action of potassium-sparing diuretics, which makes it necessary to monitor the serum levels of potassium. Concurrent treatment with other types of antiphlogistics may increase the risk of side effects. The same applies as for other analgesics: If patients with acute abdominal pain are given repeated pain relief, the symptom picture of any complications, such as perforation, may be changed or masked.

Hepatic effects:

Hepatitis can occur without prodromal symptoms.

Elevations of one or more liver tests may occur during therapy with diclofenac sodium. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e. less than 3 times the ULN [ULN = the upper limit of normal range]) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open-label, controlled trial of 3,700 patients treated for 2-6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST were observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), diclofenac sodium should be discontinued immediately. To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

To minimize the potential risk for an adverse liver related event in patients treated with diclofenac sodium, the

lowest effective dose should be used for the shortest duration possible. Caution should be exercised in prescribing diclofenac sodium with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

Cardiovascular and cerebrovascular effects:

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.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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.

Dermatological:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest risk for 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. Swiss Relief Dual Release should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Female fertility:

The use of Swiss Relief Dual Release 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 Swiss Relief Dual Release should be considered.

Swiss Relief Dual Release, in common with other NSAIDs, can reversibly inhibit platelet aggregation.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions:

The dicumarol group and ticlopidine. NSAIDs block the aggregation of thrombocytes and damage the mucosa in the gastrointestinal tract. In addition, diclofenac may block the metabolism of warfarin, thereby increasing the levels of warfarin in the plasma. The risk of bleeding increases in patients receiving anticoagulants concurrently with diclofenac. The risk of a bleeding stomach ulcer is greater with concomitant use of NSAIDs and anticoagulants. The combination should be avoided.

Heparin (parenteral application): Increased risk of bleeding (inhibition of the thrombocyte function and increased gastrointestinal side effects of NSAIDs).

Pentoxifylline: Increased risk of bleeding, intensified clinical monitoring and control of bleeding time recommended.

Zidovudine: Increased toxicity on red blood cells resulting in severe anemia.

Corticosteroids and alcohol: Both may increase the toxicity of diclofenac (increase of ulcerogenic effects).

Diuretics. NSAIDs can counteract the diuretic and antihypertensive effects of thiazides, thiazide-related diuretics, and loop diuretics. A dose adjustment of these agents may be necessary. Diuretics can increase the risk of nephrotoxicity of NSAIDs. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored.

Antihypertensive agents. Antihypertensives of the NSAID type counteract the antihypertensive effect of beta-receptor blockers and ACE blockers. A dose adjustment of the antihypertensive agent may therefore be necessary.

Other analgesics including cyclo-oxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.

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

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

Pharmacodynamic studies have shown no potentiation of oral hypoglycaemic drugs, but caution and adequate monitoring are nevertheless advised.

Caution should be exercised in prescribing diclofenac sodium with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

Pharmacokinetic interactions:

The actions of diclofenac on the pharmacokinetics of other medicaments:

Methotrexate. NSAIDs block the tubular secretion of methotrexate, with increased plasma concentrations as the outcome. High-dose treatment with methotrexate should be avoided with concurrent use of diclofenac. Care should be exercised with concurrent low-dose treatment and the patients should be monitored with respect to methotrexate-related toxicity.

Lithium. Diclofenac reduces the renal clearance of lithium by about 20% and thus increases the lithium concentrations in serum. Adjustment of the lithium dose may be necessary. The combination should be avoided if the serum content of lithium cannot be monitored regularly on institution or termination of the treatment.

Cyclosporin and tacrolimus. With concurrent treatment with diclofenac and cyclosporin (in rheumatoid arthritis), a relatively high frequency of nephrotoxicity (increased serum creatinine) with a rise in blood pressure has been seen. This risk is probably also present with concurrent tacrolimus treatment. After an oral single dose of cyclosporin during on-going diclofenac treatment, the plasma concentration of diclofenac was also doubled. The combination should be given with caution. In the case of combination treatment, the diclofenac dose should be halved.

Digoxin. Studies of healthy volunteers show that institution of diclofenac in persons using digoxin leads to rises in the digoxin content in plasma. The plasma concentrations of digoxin should be monitored on institution and termination of diclofenac. A dose adjustment may be necessary.

The actions of other medicaments on the pharmacokinetics of diclofenac:

Medicaments that block the enzyme, CYP 2C9. The metabolism of diclofenac is catalysed by the enzyme, CYP 2C9. Concurrent treatment with medicaments that block this enzyme (such as fluconazole) probably leads to higher plasma concentrations of diclofenac. Medicaments that induce CYP 2C9, such as rifampicin, carbamazepine, or barbiturates may reduce the plasma concentrations of diclofenac to subtherapeutic levels. Diazepam, which is metabolised via CYP 2C19, increased the plasma concentrations of diclofenac by 50-100%.

Colestipol and colestyramine. Concurrent administration of diclofenac and colestipol or colestyramine reduces the absorption of diclofenac by about 30%, respectively 60%. The medicaments should be given at intervals of several hours.

4.6 Pregnancy and lactation

Pregnancy: Congenital abnormalities have been reported in association with NSAID administration in man, however these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation: Diclofenac crosses into breast-milk in very low concentrations. NSAIDs should, if possible, be avoided when breast-feeding.

4.7 Effects on ability to drive and use machines

In some patients, treatment with Swiss Relief Dual Release Capsules can reduce the ability to react. This should be taken into account when special alertness is required, for instance in driving vehicles.

4.8 Undesirable effects

Common: (>1/100)

General: Headache. Dizziness or vertigo.

Gastrointestinal: Epigastric pain. Nausea. Vomiting. Diarrhoea. Abdominal pain. Dyspepsia. Flatulence. Anorexia.

Skin: Rash.

Liver: Elevated transaminases (ASAT, ALAT).

Less common: (< 1/100, > 1/1000)

General: Tiredness. Oedema. Hypersensitivity reactions (for instance bronchospasm, anaphylactic reactions, including hypotension). Hypertension.

Gastrointestinal: Gastrointestinal bleeding. Haematemesis. Melaena. Peptic ulcer with or without bleeding or perforation. Bloody diarrhoea.

Skin: Urticaria.

Liver: Disturbances of liver function, including hepatitis with or without icterus.

Airway: Bronchospasm. Asthma.

Others: Cardiac insufficiency. Thrombophlebitis.

Rare: (<1/1000)

General: Impotence (the relation is doubtful).

Blood: Thrombocytopenia. Leucopenia. Agranulocytosis. Haemolytic anaemia. Aplastic anaemia.

CNS: Paraesthesias. Memory disturbances. Disorientation. Impaired hearing and sight disturbances (clouded vision, double vision). Buzzing in the ears. Sleep difficulties. Somnolence. Irritability. Convulsions. Depression. Anxiety. Nightmares. Tremor. Psychotic reactions. Taste changes. Aseptic Meningitis.

Gastrointestinal: Peptic ulcer with perforation, diaphragm-like intestinal strictures. Disorders of the large intestine (non-specific haemorrhagic colitis and exacerbation of ulcerous colitis or Crohn's proctocolitis). Aphthous stomatitis. Glossitis. Oesophageal lesions. Constipation. Pancreatitis).

Skin: Bullous eruptions. Eczema. Erythema multiforme. Stevens-Johnson syndrome. Lyell's disease (acute toxic epidermolysis). Erythroderma (exfoliative dermatitis). Loss of hair. Light hypersensitivity reactions. Photosensibilisation. Purpura.

Liver: Fulminant hepatitis.

Neurological: Loss of feeling.

Urogenital: Acute renal insufficiency. Haematuria. Proteinuria. Interstitial nephritis. Nephrotic syndrome. Papillary necrosis.

Other: Palpitations. Chest pains. Peripheral oedema. Pneumopatic hypersensitivity.

Gastrointestinal bleeding or ulceration/perforation in general gives more serious consequences in the elderly. This can occur at any time during treatment, with or without warning signs or a history of disease.

Diclofenac temporarily blocks the thrombocyte aggregation, which may lead to increased risk in patients with various bleeding diseases.

4.9 Overdose

Symptoms: Nausea, vomiting, abdominal pains. Cerebral symptoms (dizziness, somnolence, headache, tinnitus, anxiety, hallucinations). Effects on the kidneys. Tendency to oedema, possibly metabolic acidosis.

Treatment: If justified, gastric lavage, charcoal. Antacids, as needed, which can be supplemented by sucralfate. Good diuresis must be ensured. Symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: M01A B05

Diclofenac is a non-steroidal substance with anti-inflammatory, analgesic, and antipyretic properties. It blocks the prostaglandin synthesis. Experiments have shown that blockade of the prostaglandin synthesis is an important part of the mechanism of action. Prostaglandins play a major role in inflammation, pain, and fever. This means that diclofenac blocks thrombocyte aggregation. In rheumatic disease, diclofenac has anti-inflammatory and analgesic effects, which are clinically characterised by alleviation of such symptoms as pain at rest and on movement, reduced morning stiffness and swelling of joints, and improved function. Diclofenac has been shown to relieve pain and reduce the amount of bleeding in dysmenorrhoea. Diclofenac blocks the renal synthesis of prostaglandin. In patients with normal kidney function this effect is of no significant clinical importance. In patients with chronic kidney, heart, or liver insufficiency and with changes in the plasma volume, blockade of the prostaglandin synthesis may lead to acute renal insufficiency, retention of fluid, and heart failure.

Diclofenac blocks the aggregation of thrombocytes.

5.2 Pharmacokinetic properties

Diclofenac sodium is rapidly absorbed from the gut and is subject to first-pass metabolism. Therapeutic plasma concentrations occur about ½ hour after administration of Swiss Relief Dual Release. The active substance is 99.7%

protein bound and the plasma half-life for the terminal elimination phase is 1-2 hours. Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. The remainder of the dose is excreted via the bile in metabolised form.

Following rapid gastric passage, the enteric coated pellet component of Swiss Relief Dual Release ensures quick availability of the active component in the blood stream. The sustained release pellets cause a delayed release of the active component, which means one single daily dose is usually sufficient.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Talc, microcrystalline cellulose, povidone K 25, colloidal anhydrous silica, propylene glycol, poly[ethylacrylate-co-methylmethacrylate-co-(2-trimethylammonioethyl)methacrylate chloride] (1:2:0.1), poly[ethylacrylate-co-methylmethacrylate-co-(2-trimethylammonioethyl)methacrylate chloride] (1:2:0.2), methacrylic acid-ethylacrylate-copolymer (1:1) (Ph. Eur.), dibutyl phthalate, gelatin, indigo carmine (E 132), titanium dioxide (E 171), sodium lauryl sulfate, printing ink.

6.2 Incompatibilities

Not relevant.

6.3 Special precautions for storage

Store below 25°C.

6.4 Nature and contents of container

Blister packs: 20 capsules.

6.5 Instructions for use/handling

No special instructions.

7. MANUFACTURER

Temmler Werke GmbH, Weißenstephaner Str. 28, 81673 Munich, Germany.

8. LICENSE HOLDER

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