NOVARTIS

Voltaren®
Voltaren® Retard

Composition

Active substances

Gastro-resistant tablets: Diclofenac sodium (phenylacetic acid derivative)

Prolonged release tablets (Voltaren Retard): Diclofenac sodium (phenylacetic acid derivative)

Suppositories: Diclofenac sodium (phenylacetic acid derivative)

Oral drops: Diclofenac resinate, equivalent to diclofenac sodium

Excipients

Gastro-resistant tablets:

Core for 25 mg and 50 mg: Cellulose microcrystalline; lactose monohydrate; magnesium stearate; maize starch; povidone; silica, colloidal anhydrous; sodium starch glycolate (type A);

Coating for 25 mg: hypromellose; iron oxide yellow (E172); macrogoglycerol hydroxystearate; Methacrylic acid – ethyl acrylate copolymer; macrogol 8000; talc; titanium dioxide (E171); Simeticone; alpha-octadecyl-omega-hydroxy-polyglykolether; sorbic acid.

Coating for 50 mg: hypromellose; iron oxide red (E172); iron oxide yellow (E172); macrogoglycerol hydroxystearate; Methacrylic acid – ethyl acrylate copolymer; macrogol 8000; talc; titanium dioxide (E171); Simeticone; alpha-octadecyl-omega-hydroxy-polyglykolether; sorbic acid.

Prolonged-release tablets:

Tablet core: Cetyl alcohol; magnesium stearate; povidone; silica; colloidal anhydrous; sucrose;

Tablet coating: hypromellose; iron oxide red (E172); macrogol 8000; polysorbate 80; sucrose; talc; titanium dioxide (E171); Printing ink: Carbon black, Shellac, Ammonium hydroxide, Simethicone

Suppositories: Hard fat.

Oral drops:

Castor oil, hydrogenated powder; paraffin liquid; saccharin sodium; copolymer of acrylic and methacrylic acid with divinylbenzene and ethylvinylbenzene (Zerolite 236 SRC 48), washed; tutti-frutti flavour.

Information might differ in some countries.

Sodium content per dosage unit:

	Sodium content per unit
25 mg gastro-resistant coated tablet	2.355 mg/gastro-resistant coated tablet
50 mg gastro-resistant coated tablet	4.16 mg/gastro-resistant coated tablet
75 mg prolonged-release tablet	5.415 mg/prolonged-release tablet
100 mg prolonged-release tablet	7.22 mg/prolonged-release tablet
12.5 mg/1 g suppositories	0.91 mg/suppository
25 mg/1 g suppositories	1.81 mg/suppository
50 mg/2 g suppositories	3.62 mg/suppository
100 mg/2 g suppositories	7.23 mg/suppository
Drops	1.86 mg/ml equivalent to 0.06 mg/gtt.

Pharmaceutical form and quantity of active substance per unit

Gastro-resistant tablets containing 25 mg/50 mg

Prolonged release tablets containing 75 mg/100 mg

Suppositories containing 12.5 mg/25 mg/50 mg/100 mg

Oral drops equivalent to 15 mg diclofenac sodium per ml (1 drop = 0.5 mg diclofenac sodium)

Indications/Potential uses

Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis including spondylarthritis

Painful syndromes of the vertebral column.

Non-articular rheumatism.

Painful post-traumatic and post-operative inflammation and swelling, e.g. following dental or orthopaedic surgery.

Painful and/or inflammatory gynaecological conditions, e.g. primary dysmenorrhoea or adnexitis.

Migraine attacks (suppositories).

Acute attacks of gout (gastro-resistant tablets, suppositories, oral drops).

As an adjunct in acute painful inflammatory infections of the ear, nose or throat, e.g. pharyngotonsillitis, otitis (gastro-resistant tablets, suppositories, oral drops).

In keeping with standard therapeutic principles, the underlying disease should be treated with specific therapy as appropriate. Fever alone is not an indication.

Dosage/Administration

As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see "Warnings and precautions").

Usual dosage

Adults

Gastro-resistant tablets, suppositories

The starting dose for Voltaren gastro-resistant tablets and Voltaren suppositories is usually 100-150 mg/day. In milder cases and for long-term therapy, 75-100 mg/day are normally sufficient.

The total daily amount is generally given in 2–3 divided doses. In order to avoid nocturnal pain and morning stiffness, treatment with the gastro-resistant tablets during the daytime can be supplemented by the administration of a suppository at bedtime (up to a maximum daily dose of 150 mg).

In primary dysmenorrhoea, the daily dosage should be individually adjusted and is generally 50-150 mg/day. Treatment should be started at 50-100 mg/day and, if necessary, may gradually be increased over the course of several menstrual cycles to a maximum of 150 mg/day.

The gastro-resistant tablets should be swallowed with liquid, preferably before meals; they must not be divided or chewed.

The suppositories should be inserted well into the rectum, preferably after a bowel movement.

Treatment of migraine attacks with Voltaren suppositories should be started with a dose of 100 mg at the first sign of an impending attack. Additional suppositories up to a maximum of 50 mg may be taken on the same day, if required. If further treatment is required on the following day, the maximum daily dosage should be limited to 150 mg, given in divided doses.

Prolonged release tablets

The usual daily dose of Voltaren Retard is 100-150 mg, i.e. one 100 mg prolonged release tablet, or two 75 mg prolonged release tablets. In milder cases and for long-term therapy, one 75 mg or 100 mg prolonged release tablet per day is normally sufficient. If symptoms are most pronounced at night or in the morning, the tablets should preferably be taken in the evening. The prolonged release tablets should be swallowed whole with liquid, preferably with meals.

Special dosage instructions

Established cardiovascular disease or significant cardiovascular risk factors

Treatment with Voltaren is generally not recommended in patients with established cardiovascular disease or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease should be treated with Voltaren only after careful consideration, and only at doses of up to 100 mg daily if treated for more than 4 weeks (see "Warnings and precautions").

Patients with hepatic impairment

Voltaren is contraindicated in patients with hepatic failure (see "Contraindications").

No specific studies have been carried out in patients with hepatic impairment; therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Voltaren to patients with mild to moderate hepatic impairment (see "Warnings and precautions").

Patients with renal impairment

Voltaren is contraindicated in patients with renal failure (GFR <15 ml/min/1.73 m^2; see "Contraindications").

No specific studies have been carried out in patients with renal impairment; therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Voltaren to patients with renal impairment (see "Warnings and precautions").

Elderly patients

No adjustment of the starting dose is generally required for elderly patients. However, caution is indicated on basic medical grounds, especially for frail elderly patients or those with a low body weight (see "Warnings and precautions").

Children and adolescents

Voltaren oral drops are particularly suitable for paediatric use since they enable the dosage to be individually tailored to body weight within the recommended range (1 drop = 0.5 mg).

For adolescents and for children aged 1 year or older, the daily dosage, depending on the severity of the disorder, is 0.5 to 2 mg/kg body weight, given in 2-3 divided doses. For the treatment of juvenile rheumatoid arthritis, the daily dosage can be increased up to a maximum of 3 mg/kg body weight, given in several divided doses.

The maximum daily dose of 150 mg should not be exceeded.

The bottle containing the suspension should always be shaken thoroughly before the drops are administered.

Voltaren must not be given to children under 1 year of age.

Voltaren 50 mg gastro-resistant tablets and Voltaren 50 mg and 100 mg suppositories are not recommended for use in children due to their dosage strength.

Voltaren 25 mg gastro-resistant tablets may be used in these patients.

Voltaren 75 mg and 100 mg prolonged release tablets are not suitable for children and adolescents.

Voltaren 12.5 mg or 25 mg suppositories are recommended for use in children and adolescents below 14 years of age. Due to their dosage strength, Voltaren 50 mg suppositories are not recommended in children and adolescents below 14 years of age. Voltaren 100 mg suppositories are not suitable for children and adolescents.

Contraindications

Hypersensitivity to the active substance or to any of the excipients indicated under "Composition".

A history of bronchospasm, angioedema, urticaria, acute rhinitis, nasal polyps or allergy-like symptoms after taking acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.

Third trimester of pregnancy (see "Pregnancy/Breast-feeding").

Active gastric and/or duodenal ulcers, gastrointestinal bleeding or perforation.

Inflammatory bowel disease (such as Crohn's disease or ulcerative colitis).

Hepatic failure (Child-Pugh class C) (cirrhosis of the liver and ascites).

Renal failure (GFR <15 ml/min/1.73 m^2).

Severe heart failure (NYHA III-IV).

Treatment of post-operative pain after coronary bypass surgery (or use of a heart-lung machine).

Suppositories: Proctitis.

Warnings and precautions

General warning for the use of systemic non-steroidal anti-inflammatory drugs:

Gastrointestinal ulceration, bleeding or perforation may occur at any time during treatment with non-steroidal anti-inflammatory drugs (NSAIDs), whether COX-2 selective or not, even in the absence of warning symptoms or a predisposing history. To minimise this risk, the lowest effective dose should be given for the shortest possible duration of treatment.

Placebo-controlled studies have shown an increased risk of thrombotic cardiovascular and cerebrovascular complications with certain COX-2 selective inhibitors. It is not yet known whether this risk correlates directly with the COX-1 / COX-2 selectivity of individual NSAIDs. As no comparable clinical study data are available at present for long-term treatment with the maximum dosage of diclofenac, the possibility of a similarly elevated risk cannot be ruled out. Until such data becomes available, a careful risk-benefit assessment must be carried out prior to using diclofenac in patients with clinically confirmed coronary heart disease, cerebrovascular disorders, peripheral arterial occlusive disease or considerable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking). Due to this risk, too, the lowest effective dose should be given for the shortest possible duration of treatment.

The renal effects of NSAIDs include fluid retention with oedema and/or arterial hypertension. For this reason, diclofenac should be used with caution in patients with cardiac impairment and other conditions that predispose to fluid retention. Caution is also indicated in patients who take concomitant diuretics or ACE inhibitors, or who are at increased risk of hypovolaemia.

The consequences are generally more serious in the elderly. If gastrointestinal bleeding or ulceration occurs in patients undergoing treatment with Voltaren, the medicinal product should be withdrawn.

Cutaneous reactions

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, including Voltaren (see "Adverse effects"). Patients appear to be at highest risk at the start of treatment, with the onset of the reaction usually occurring within the first month of treatment. Voltaren should be discontinued at the first sign of rash, mucosal lesions or any other sign of hypersensitivity.

As with other NSAIDs, allergic reactions – including anaphylactic/anaphylactoid reactions – may occur in rare cases, even without prior exposure to diclofenac.

Masking signs of infection

Its pharmacodynamic properties mean that, like other NSAIDs, diclofenac may mask the signs and symptoms of infection.

Precautions

General

The concomitant use of Voltaren with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the potential for additive adverse effects (see "Interactions").

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

Voltaren gastro-resistant tablets contain lactose. Patients with rare hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Voltaren gastro-resistant tablets.

Voltaren Retard tablets contain sucrose and are therefore not recommended in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency.

This medicine contains less than 1 mmol (23 mg) of sodium per dosage unit (coated tablet, prolonged-release tablet and drops), making it practically "sodium-free".

Voltaren coated tablets contain poly(oxyethylene)-40 castor oil and may cause stomach upset and diarrhoea.

Voltaren drops contain hydrogenated castor oil and may cause stomach upset and diarrhoea.

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 to NSAIDs such as asthma exacerbations (analgesic intolerance or analgesic-induced asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, particular caution is required in such patients (emergency readiness). This also applies to patients with allergic reactions – e.g. rash, pruritus or urticaria – to other substances.

Gastrointestinal effects

As with all NSAIDs, including diclofenac, close medical surveillance is required and particular caution should be exercised when prescribing Voltaren in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see "Adverse effects"). The risk of GI bleeding is greater with higher NSAID doses and in patients with a history of ulcers (particularly if complicated by bleeding or perforation) and in elderly patients.

Treatment should be initiated and maintained at the lowest effective dose in order to reduce the risk of GI toxicity in patients with a history of ulcers (particularly if complicated by bleeding or perforation) and in elderly patients.

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 elderly patients, should report any unusual abdominal symptoms (especially GI bleeding). Caution is required in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, antiplatelet agents or selective serotonin reuptake inhibitors (see "Interactions").

NSAIDs, including diclofenac, can be associated with an increased risk of a gastrointestinal anastomosis leak. Caution is required with the use of Voltaren after gastrointestinal surgery and close medical monitoring is recommended.

Hepatic effects

Close medical surveillance is required when giving Voltaren / Voltaren Retard to patients with hepatic impairment, as their condition might be exacerbated (see "Adverse effects").

As with all NSAIDs, including diclofenac, levels of one or more liver enzymes may rise during treatment with Voltaren / Voltaren Retard. This has been observed very frequently with diclofenac in clinical studies (in approximately 15% of patients), but is very rarely accompanied by clinical symptoms. Most of these cases involve borderline increases. Frequently (in 2.5% of cases) the increases observed were moderate (≥ 3 to < 8 times the upper limit of normal), while the incidence of marked increases (≥ 8 times the upper limit of normal) remained around 1%. Elevated liver enzyme levels were accompanied by clinically manifest liver damage in 0.5% of cases in the above-mentioned clinical studies. Elevated enzyme levels were generally reversible after discontinuation of the drug. As with other NSAIDs, long-term treatment with Voltaren / Voltaren Retard calls for regular monitoring of liver enzyme levels.

Voltaren/Voltaren Retard should be discontinued if abnormal liver function tests persist or worsen, if clinical signs or symptoms suggestive of liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash). In addition to elevated liver enzymes, there have been rare reports of severe hepatic reactions, including jaundice and fulminant hepatitis, hepatic necrosis and hepatic failure which, in isolated cases, had a fatal outcome. Hepatitis may develop without prodromal symptoms. Caution is required when using Voltaren/Voltaren Retard in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

Owing to the importance of prostaglandins in maintaining renal blood flow, prolonged treatment with high doses of NSAIDs, including diclofenac, frequently (1–10%) results in oedema and hypertension. Particular caution is required in patients with impaired cardiac or renal function, in patients with a history of hypertension, in elderly patients, in patients receiving concomitant treatment with diuretics or medicinal products that may significantly impact renal function, and in patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see "Contraindications"). Monitoring of renal function is recommended as a precautionary measure when using Voltaren in such cases. Patients usually recover to their pre-treatment state following discontinuation of therapy.

Cardiovascular effects

Treatment with NSAIDs including diclofenac, particularly at high doses and for prolonged periods, may be associated with a slightly increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke). Treatment with Voltaren is generally not recommended in patients with established cardiovascular disease (heart failure, established ischaemic 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 Voltaren only after careful consideration and only at doses of up to 100 mg daily if treated 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 arterial thromboembolic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warning. Patients should be instructed to see a physician immediately in case of such an event.

Haematological effects

As with other NSAIDs, complete blood counts are recommended during long-term treatment with Voltaren / Voltaren Retard.

Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation. Patients with coagulation disorders should be closely monitored.

Interactions

The following interactions were observed with Voltaren / Voltaren Retard and/or other dosage forms of diclofenac.

Observed interactions to be considered

Enzyme inducers

CYP2C9 inducers

Caution is required when co-administering diclofenac with CYP2C9 inducers (such as rifampicin). This could result in a significant decrease in plasma concentration and exposure to diclofenac.

Enzyme inhibitors

CYP2C9 inhibitors

Caution is required when co-administering diclofenac with CYP2C9 inhibitors (such as voriconazole). This could result in a significant increase in peak plasma concentrations and exposure to diclofenac.

Lithium

Diclofenac may increase plasma concentrations of co-administered lithium. Monitoring of serum lithium levels is recommended.

Digoxin

Diclofenac may increase plasma concentrations of co-administered digoxin. Monitoring of serum digoxin levels is recommended.

Diuretics and antihypertensive agents

As with other NSAIDs, co-administration of diclofenac may reduce the antihypertensive effects of diuretics or antihypertensive agents (e.g. beta blockers, angiotensin-converting-enzyme [ACE] inhibitors). The combination should therefore be administered with caution, and patients – especially elderly patients – should have their blood pressure monitored regularly. Patients should be adequately hydrated, and attention should be paid to monitoring renal function on initiating combination therapy, and regularly thereafter, particularly with diuretics and ACE inhibitors due to the increased risk of nephrotoxicity (see "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. It should therefore be given at doses lower than those that would be used in patients not receiving ciclosporin or tacrolimus.

Drugs known to cause hyperkalaemia

Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased plasma potassium levels, which should therefore be monitored frequently (see "Warnings and precautions").

Quinolone antibiotics

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

Anticipated interactions to be considered

Other NSAIDs and corticosteroids

Concomitant administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal adverse effects (see "Warnings and precautions").

Anticoagulants and antiplatelet agents

Caution is required since co-administration could increase the risk of bleeding (see "Warnings and precautions").

Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there have been reports of an increased risk of bleeding in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs)

Co-administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see "Warnings and precautions").

Anti-diabetic agents

Clinical studies have shown that diclofenac can be given together with oral anti-diabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic reactions following administration of diclofenac, requiring adjustment of the dosage of the anti-diabetic agent. For this reason, monitoring of blood glucose levels is recommended as a precautionary measure during combination therapy.

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

Methotrexate

Caution is required when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate because blood levels of methotrexate may rise, and methotrexate toxicity may increase.

Phenytoin

Monitoring of phenytoin plasma concentrations is recommended if phenytoin is used concomitantly with diclofenac due to an expected increase in exposure to phenytoin.

Pregnancy/Breast-feeding

Pregnancy

Inhibition of prostaglandin synthesis may have a negative impact on pregnancy and/or embryofetal development. Data from epidemiological studies suggest an elevated risk of miscarriage and of cardiac malformation and gastroschisis following administration of a prostaglandin synthetase inhibitor during early pregnancy. The risk is assumed to rise with the dose and the duration of therapy.

In animals, administration of a prostaglandin synthetase inhibitor has been shown to result in increased pre-implantation and post-implantation loss and embryofetal lethality. In addition, increased incidences of various malformations, including cardiovascular malformations, have been reported in animals given a prostaglandin synthetase inhibitor during organogenesis (see "Preclinical data").

First/second trimester

During the first and second trimesters of pregnancy, diclofenac should not be given unless absolutely necessary. If diclofenac is used by a woman attempting to conceive, or during the first or second trimesters of pregnancy, the dose should be kept as low – and the duration of treatment as short – as possible.

Third trimester

Diclofenac is contraindicated during the third trimester of pregnancy. All prostaglandin synthetase inhibitors may:

- expose the fetus to the following risks:

cardiopulmonary toxicity (with premature closure of the ductus arteriosus, and pulmonary hypertension, also see "Preclinical data");

renal dysfunction, which may progress to renal failure with oligohydramnios.

- expose the mother and child to the following risks:

possible prolongation of bleeding time, an effect of inhibition of platelet aggregation even at very low doses; inhibition of uterine contractions, resulting in delayed or prolonged labour.

Breast-feeding

As with other NSAIDs, small amounts of diclofenac pass into the breast milk. As a precaution, diclofenac should therefore not be used by women who are breast-feeding. If treatment is essential, the infant should be switched to bottle feeding.

Fertility

Diclofenac may impair female fertility and is therefore not recommended in women attempting to conceive. Consideration should be given to stopping diclofenac in women who are having difficulty conceiving, or in those being tested for infertility.

In animals, based on relevant data, impairment of male fertility cannot be ruled out (see "Preclinical data"). The relevance of this finding for humans is unclear.

Effects on the ability to drive and to use machines

Patients experiencing visual disturbances, light-headedness, dizziness, drowsiness or other central nervous system disturbances while taking Voltaren / Voltaren Retard should refrain from driving or using machines.

Adverse effects

The following adverse effects include those reported with Voltaren/ Voltaren Retard and/or other dosage forms of diclofenac during either short-term or long-term use.

Frequencies

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

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: Angioedema (including facial oedema).

Psychiatric disorders

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

Nervous system disorders

Common: Headache, light-headedness.

Rare: Somnolence.

Very rare: Paraesthesia, memory impairment, convulsions, anxiety, tremor, aseptic meningitis, dysgeusia, cerebrovascular accident.

Eye disorders

Very rare: Visual disturbances, visual impairment, diplopia.

Ear and labyrinth disorders

Common: Vertigo.

Very rare: Tinnitus, impaired hearing.

Cardiac disorders

Uncommon:* Myocardial infarction, heart failure, palpitations, chest pain.

Not known: Kounis syndrome.

Vascular disorders

Common: Hypertension.

Very rare: 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, melaena, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis or perforation, which may lead to peritonitis). Suppositories: Proctitis.

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

Voltaren Retard may provoke chronic inflammatory conditions with pseudomembranes and strictures in the lower intestines (small and large intestines).

Hepatobiliary disorders

Common: Increased transaminases.

Rare: Hepatitis, jaundice, hepatic dysfunction.

Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure.

Skin and subcutaneous tissue disorders

Common: Rash.

Rare: Urticaria.

Very rare: Bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schoenlein purpura, pruritus.

Renal and urinary disorders

Common: Fluid retention, oedema.

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

General disorders and administration site conditions

Common: Suppositories: local irritation.

Rare: Oedema.

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

Meta-analyses of controlled clinical studies and pharmacoepidemiological data point towards an increased risk of arterial thromboembolic events (for example, myocardial infarction or stroke) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment (see "Warnings and precautions").

Description of selected adverse effects

Visual effects

Visual disturbances such as visual impairment, blurred vision and 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.

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product.

Overdose

Signs and symptoms

There is no typical clinical picture following diclofenac overdose. Overdose may cause symptoms such as vomiting, gastrointestinal bleeding, diarrhoea, light-headedness, tinnitus or convulsions. Acute renal failure and liver damage are possible in the event of severe intoxication.

Treatment

Treatment of acute intoxication 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 disorders and respiratory depression.

Specific measures such as forced diuresis, dialysis or haemoperfusion are unlikely to be helpful in eliminating NSAIDs, including diclofenac, due to their 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.

Properties/Actions

ATC code:

M01AB05

Mechanism of action

Voltaren contains the sodium salt of diclofenac, a non-steroidal agent with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic activity.

Inhibition of prostaglandin biosynthesis has been demonstrated experimentally and is considered fundamental to the mechanism of action of diclofenac. Prostaglandins play a major role in causing inflammation, pain and fever. *In vitro*, at concentrations equivalent to those attained in humans, Voltaren does not suppress proteoglycan biosynthesis in cartilage.

Pharmacodynamics

See "Mechanism of action"

Clinical efficacy

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterised by improved function and marked relief of signs and symptoms such as pain at rest, pain on movement, morning stiffness and swelling of the joints. In post-traumatic and post-operative inflammatory conditions, Voltaren rapidly relieves both spontaneous pain and pain on movement, and reduces inflammatory swelling and wound oedema.

In clinical trials, the product has also been shown to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. It can relieve the pain, and also reduce bleeding, in primary dysmenorrhoea. Voltaren (suppositories) also has a beneficial effect on the symptoms of migraine attacks.

Pharmacokinetics

Absorption

Gastro-resistant tablets

Diclofenac is completely absorbed from the gastro-resistant tablets after their passage through the stomach. Although absorption is rapid, its onset may be delayed due to the gastro-resistant coating of the tablet. Mean peak plasma concentrations of 1.5 μg/ml are attained on average 2 hours after administration of a 50 mg tablet. The tablets pass through the stomach more slowly when ingested with or after a meal than when ingested before a meal, but the amount of diclofenac absorbed remains the same.

Prolonged release tablets

Judged on the basis of the urinary recovery of unchanged diclofenac and its hydroxylated metabolites, the same amount of diclofenac is released and absorbed from Voltaren Retard as from the gastro-resistant tablets. However, on average the systemic bioavailability of diclofenac from Voltaren Retard is approximately 82% of that attained with the same dose of Voltaren administered in the form of gastro-resistant tablets (possibly due to release-rate-dependent first-pass metabolism). Owing to the slower release of the active substance from Voltaren Retard, peak plasma concentrations are lower than with the gastro-resistant tablets.

Mean peak plasma concentrations of 0.5 μg/ml and 0.4 μg/ml are attained on average 4 hours after administration, respectively, of 100 mg or 75 mg prolonged release tablets. Ingestion with food has no notable effect on the absorption and systemic bioavailability of Voltaren Retard.

On the other hand, mean plasma concentrations of 13 ng/ml are recorded 24 hours (16 hours) after ingestion of 100 mg (75 mg).

Ingestion of 100 mg once daily or 75 mg twice daily produces trough plasma levels of approximately 22 ng/ml and 25 ng/ml, respectively.

Suppositories

The onset of absorption of diclofenac from suppositories is rapid, although the rate of absorption is slower than from orally administered gastro-resistant tablets. On average, peak plasma concentrations are attained within 1 hour of administration of 50 mg suppositories, but the peak plasma concentrations per dose unit are about two-thirds of those reached following administration of gastro-resistant tablets.

Oral drops

Diclofenac is absorbed completely from the resinate suspension. Absorption begins immediately after administration, but is slower than absorption from gastro-resistant tablets. The amount absorbed is similar, but peak plasma concentrations are only one-third of those achieved following administration of gastro-resistant tablets.

Peak plasma concentrations of approximately 0.5 μg/ml are attained within two hours of oral ingestion of a single dose of oral drops equivalent to 50 mg diclofenac sodium.

Since about half the absorbed diclofenac is metabolised during 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 with repeated administration. No accumulation occurs provided the recommended dosing intervals are observed. Plasma concentrations attained in children after equivalent doses (mg/kg body weight) are similar to those attained in adults.

Distribution

Diclofenac is 99.7% bound to serum proteins, mainly albumin (99.4%).

The apparent volume of distribution has been calculated at 12-0.17 litres/kg.

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after peak plasma values have been reached. The apparent elimination half-life from the synovial fluid is 3-6 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.

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

Metabolism

Biotransformation of diclofenac is partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation. This results in several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are subsequently converted to glucuronide conjugates. Two of these phenolic metabolites are pharmacologically active, but to a much lesser extent than diclofenac itself.

Elimination

Total systemic clearance of diclofenac from plasma is 263 ± 56 ml/minute (mean value ± SD). The terminal half-life is 1-2 hours. Four of the metabolites, including the two that are active, also have short half-lives of 1-3 hours. The virtually inactive metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a much longer half-life.

About 60% of the dose is excreted in the urine as metabolites, compared with less than 1% as unchanged substance. The rest of the dose is eliminated as metabolites via the bile in the faeces.

Linearity/non-linearity

The amount absorbed is in linear proportion to the size of the dose.

Pharmacokinetics in special populations

No relevant age-dependent differences in absorption, metabolism or excretion have been observed.

Hepatic impairment

In patients with hepatic impairment (chronic hepatitis or compensated cirrhosis), the pharmacokinetics and metabolism of diclofenac are the same as in patients without liver disease.

Renal impairment

In patients with renal impairment, the drug's single-dose pharmacokinetics do not suggest any accumulation of unchanged active substance with the usual dosage schedule. In patients with a creatinine clearance of <10 mL/min, theoretical steady-state plasma levels of the metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared via the bile.

Preclinical data

Preclinical data from safety pharmacology studies, acute and repeated dose toxicity studies and genotoxicity, mutagenicity and carcinogenicity studies with diclofenac revealed no evidence of a specific hazard for humans at the intended therapeutic doses.

The increased incidence of lymphomas (thymus) in mice, and subcutaneous fibromas, fibroadenomas (mammary gland) or C-cell adenomas (thyroid gland) in rats were all within the historical control range of the laboratory for the animal strain used, and are considered to have occurred by chance.

In all toxicity studies carried out in rats, hypertrophy of mesenteric lymph nodes or lymphadenitis with reactive hyperplasia were observed. These changes were accompanied by neutrophilia that was also observed in studies in monkeys. These are presumably secondary reactions to the ulcers observed in the gastrointestinal tract. In a two-year study, a dose-dependent increase in thrombotic vascular occlusions in the heart was observed in rats treated with diclofenac.

Reproductive toxicity

Additional studies indicate that, with repeated oral doses in rats (> 1 mg/kg body weight), diclofenac causes effects that influence fertility (lower testosterone level, and decreased epididymal and testicular weight in association with histopathological changes). Similar effects were also observed in the F1 generation following doses of ≥ 1.25 mg/kg in a two-generation study. In dogs, daily subcutaneous doses of 2 mg/kg diclofenac sodium led to an increased spermatid count. Further studies describe a decreased mating frequency in female rats following a repeated dose of ≥ 0.5 mg/kg diclofenac. For this reason, an influence on both male and female fertility cannot be ruled out.

Diclofenac crosses the placental barrier in rodents. Administration of NSAIDs (including diclofenac) inhibited ovulation in rabbits and implantation and placentation in rats, and led to premature closure of the ductus arteriosus in pregnant rats. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac on reproduction parameters and delivery as well as closure of the ductus arteriosus *in utero* are pharmacological effects of this class of prostaglandin synthetase inhibitors (see "Contraindications" and "Pregnancy/Breast-feeding").

In a study in mice, teratogenicity (cleft palate) was observed at the maternally toxic dose of 4 mg/kg. In rats and rabbits, doses up to the maternally toxic level did not lead to teratogenic effects. Delayed ossification and reduced fetal weight in a study in rabbits were the only changes observed in these investigations.

At maternally toxic doses, the perinatal and post-natal development of the offspring were impaired (fertility, see above, also birth weight and delayed post-natal growth).

Other information

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Shelf life after opening

Once opened, Voltaren drops have a proven shelf life of 6 weeks.

Special precautions for storage

Keep out of the reach of children.

Gastro-resistant and prolonged release tablets: Do not store above 30°C. Protect from moisture.

Suppositories: Do not store above 30°C.

Store oral drops in a refrigerator (2-8°C). Do not freeze.

Instructions for use and handling

Oral drops: Prior to using the oral drops, hold the bottle in your hands for 2 minutes to bring the suspension to room temperature. Shake thoroughly for 1 minute before opening. Turn the bottle upside down and count out the required number of drops into a spoon.

Suppositories should not be cut apart, as incorrect storage conditions may lead to uneven distribution of the active substance.

Pack sizes

25 mg gastro-resistant tablets: 30 and 100.

50 mg gastro-resistant tablets: 20 and 100.

75 mg prolonged-release tablets: 10, 20, 30 and 100.

100 mg prolonged-release tablets: 10, 30 and 100.

12.5 mg suppositories: 10.

25 mg suppositories: 10.

50 mg suppositories: 10 and 50.

100 mg suppositories: 5 and 50.

Oral drops equivalent to 15 mg/ml: 20 ml.

Not All pack sizes and presentations are marketed

Manufacturer

See folding box

Information last revised

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Novartis Pharma AG, Basle, Switzerland

This is a medicament

– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists