TRADE-NAME(S)

Voltaren®

Anti-inflammatory and anti-rheumatic product, non-steroid, acetic acid derivative and related substance.

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Gastro-resistant tablets.

Active substance

The active substance is diclofenac sodium.

One gastro-resistant tablet contains 50 mg of diclofenac sodium.

EXCIPIENTS

Core for 50 mg: colloidal anhydrous silica, lactose, maize starch, sodium starch glycollate, povidone, microcrystalline cellulose, magnesium stearate.

Coating for 50 mg: hypromellose, yellow iron oxide (E 172), purified talc, titanium dioxide (E 171), methacrylic acid copolymer, polyethylene glycol 8000, simeticone, red iron oxide (E 172), polyoxyethylene 40 hydrogenated castor oil.

Information might differ in some countries.

INDICATIONS

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.
- Acute attacks of gout.
- Post-traumatic and post-operative pain, inflammation and swelling, e.g., following dental or orthopaedic surgery.
- Painful and/or inflammatory conditions in gynaecology, e.g., primary dysmenorrhoea or adnexitis.
- As an adjuvant in severe painful inflammatory infections of the ear, nose or throat, e.g., pharyngotonsillitis, otitis. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

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

General target population

Adults

The recommended initial daily dose is 100 to 150 mg. In milder cases, as well as for long-term therapy, 75 to 100 mg daily is usually sufficient.

The total daily dose should generally be divided into 2 to 3 doses. To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of a suppository at bedtime (up to a total maximum daily dose of 150 mg).

In primary dysmenorrhoea, the daily dose should be individually adjusted and is generally 50 to 150 mg. A dose of 50 to 100 mg should be given initially and, if necessary, increased over the course of several menstrual cycles up to a maximum of 200 mg/day. Treatment should be started on appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

Special populations

Renal impairment

Voltaren is contraindicated in patients with renal failure (GFR <15 mL/min/1.73 m^2) (see section 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 section WARNINGS AND PRECAUTIONS).

Hepatic impairment

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

Pediatric patients (below 18 years)

Children aged 1 year or over and adolescents should be given 0.5 to 2 mg/kg body weight daily in 2 to 3 separate doses, depending on the severity of the disorder. For treatment of juvenile rheumatoid arthritis, the daily dose can be raised up to a maximum of 3 mg/kg daily, given in separate doses.

Geriatric patients (65 years of age or above)

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. Although the pharmacokinetics of Voltaren are not impaired to any clinically relevant extent in elderly patients, Voltaren should be used with particular caution in such patients who generally are more prone to adverse reactions (see section WARNINGS AND PRECAUTIONS).

Established cardiovascular disease or significant cardiovascular risk factors

The use of high dose diclofenac (150mg/day) for more than 4 weeks is contraindicated in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If diclofenac treatment is needed, patients with established cardiovascular disease, uncontrolled hypertension or significant cardiovascular risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated only after careful consideration and at doses ≤100 mg daily if the treatment is for more than 4 weeks. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, diclofenac should always be prescribed at the lowest effective daily dose and for the shortest duration possible (see section WARNINGS AND PRECAUTIONS - CARDIOVASCULAR EFFECTS).

Method of administration

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

CONTRAINDICATIONS

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation (see section WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS).
- Last trimester of pregnancy (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).
- Hepatic failure.
- Renal failure. (GFR <15 mL/min/1.73 m^2).
- Severe cardiac failure (see section WARNINGS AND PRECAUTIONS).
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Voltaren is also contraindicated in patients in whom the use of acetylsalicylic acid or other NSAIDs can precipitate asthma, angioedema, urticaria, or acute rhinitis (i.e., NSAID-induced cross-reactivity reactions) (see section WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS).
- Treatment of peri-operative pain in setting of coronary artery bypass graft (CABG) surgery.
- The use of high dose diclofenac (150mg/day) for more than 4 weeks is contraindicated in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension (see sections DOSAGE AND ADMINISTRATION - SPECIAL POPULATIONS and WARNINGS AND PRECAUTIONS - CARDIOVASCULAR EFFECTS).

WARNINGS AND PRECAUTIONS

General

Voltaren gastro-resistant tablets contain lactose and therefore are not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Gastrointestinal effects

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs, including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Voltaren, the treatment should be discontinued.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative 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 section ADVERSE DRUG REACTIONS). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g., proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of –low-dose acetylsalicylic acid (ASA) or other drugs likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (see section INTERACTIONS).

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

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

Cardiovascular effects

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

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

Hematologic effects

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

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

Respiratory effects (pre-existing asthma)

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e., nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's edema or urticaria are more frequent than in other patients. Therefore, special caution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g., with skin reactions, pruritus or urticaria.

Hepatobiliary effects

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

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Voltaren (e.g., in the form of tablets or suppositories), regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g., eosinophilia, rash), Voltaren should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

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

Skin 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 section ADVERSE DRUG REACTIONS). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Voltaren should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

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

Renal effects

As fluid retention and edema have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function,

history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion of any cause, e.g., before or after major surgery (see section CONTRAINDICATIONS). Monitoring of renal function is recommended as a precautionary measure when using Voltaren in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Geriatric patients

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

Interactions with NSAIDs

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

Masking signs of infections

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

INTERACTIONS

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

Observed interactions to be considered

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

Lithium: If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g., beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity (see section WARNINGS AND PRECAUTIONS).

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

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics,

ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section WARNINGS AND PRECAUTIONS).

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

Anticipated interactions to be considered

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

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section WARNINGS AND PRECAUTIONS). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see section WARNINGS AND PRECAUTIONS).

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both 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. There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with metformin, especially in patients with pre-existing renal impairment.

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

Methotrexate: Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

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

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

There are insufficient data on the use of diclofenac in pregnant women. Some epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy, however the overall data are inconclusive. Diclofenac has been shown to cross the placental barrier in humans. Use of NSAIDs, including diclofenac,

can cause uterine inertia, premature closure of the fetal ductus arteriosus and fetal renal impairment leading to oligohydramnios.

Because of these risks, Voltaren is contraindicated in the third trimester of pregnancy (see section CONTRAINDICATIONS).

Voltaren should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. Use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.

Clinical considerations

Fetal Adverse Drug Reactions

Premature Closure of Fetal Ductus Arteriosus

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

Oligohydramnios/Fetal Renal Impairment

Risk of fetal renal impairment with subsequent oligohydramnios has been observed when NSAIDs (including diclofenac) were used from the 20th week of pregnancy onwards.

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

Labor or Delivery

There are no studies on the effects of Voltaren during labor or delivery. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia (see section CONTRAINDICATIONS). In animal studies, NSAIDS, including diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus

Published literature reports that the use of NSAIDs during the third trimester of pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Fetal Renal Impairment

Published studies and post-marketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal impairment leading to oligohydramnios. These adverse outcomes are seen, on average, after days to weeks of treatment,

although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug.

Animal Data

Reproductive and developmental studies in animals demonstrated that diclofenac administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day (0.41 times the maximum recommended human dose [MRHD] of Voltaren, 200 mg/day, based on body surface area (BSA) comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (0.41 and 0.81 times, respectively, the MRHD based on BSA comparison).

In a study in which pregnant rats were orally administered 2 or 4 mg/kg diclofenac (0.08 and 0.16 times the MRHD based on BSA) from Gestation Day 15 through Lactation Day 21, significant maternal mortality (caused by gastrointestinal ulceration and peritonitis) was noted. These maternally toxic doses were associated with dystocia, prolonged gestation, intrauterine growth retardation, and decreased fetal survival.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the fetal ductus arteriosus.

Lactation

Risk Summary

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

Human Data

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother treated orally with a diclofenac salt of 150 mg/day. The estimated dose ingested by an infant consuming breast milk is equivalent to 0.03 mg/kg/day.

Females and males of reproductive potential

Female fertility

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

Male fertility

There is no human data on the effect of Voltaren on male fertility.

Diclofenac administered to male and female rats at 4 mg/kg/day (approximately 0.16 times the MRHD based on BSA comparison) did not affect fertility.

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 1) are

are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

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

Table 1 Adverse drug reactions

Blood and lymphatic system disorders	
Very rare:	Thrombocytopenia, leukopenia, anemia (including hemolytic and aplastic anemia), agranulocytosis.
Immune system disorders	
Rare:	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare:	Angioedema (including face edema).
Psychiatric disorders	
Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common:	Headache, dizziness.
Rare:	Somnolence.
Very rare:	Paresthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, dysgeusia, cerebrovascular accident.
Eye disorders	
Very rare:	Visual impairment, blurred vision, diplopia.
Ear and labyrinth disorders	
Common:	Vertigo.
Very rare:	Tinnitus, impaired hearing.
Cardiac disorders	
Uncommon*:	Myocardial infarction, cardiac failure, palpitations, chest pain.
Frequency not known:	Kounis syndrome.
Vascular disorders	
Very rare:	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare:	Asthma (including dyspnea).
Very rare:	Pneumonitis.
Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, decreased appetite.
Rare:	Gastritis, gastrointestinal hemorrhage, hematemesis, hemorrhagic diarrhea, melena, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis, or perforation, which may lead to peritonitis).
Very rare:	Colitis (including hemorrhagic, colitis, ischemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, esophageal disorder, intestinal diaphragm disease, pancreatitis.
Hepatobiliary disorders	

Common:	Transaminases increased.
Rare:	Hepatitis, jaundice, liver disorder.
Very rare:	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common:	Rash.
Rare:	Urticaria.
Very rare:	Bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus.
Renal and urinary disorders	
Very rare:	Acute kidney injury (acute renal failure), hematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare:	Edema.

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

Description of selected adverse drug reactions

Arteriothrombotic events

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

Visual effects

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

OVERDOSAGE

Symptoms

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal hemorrhage, diarrhea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or hemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive

metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g., vomiting, gastric lavage) after ingestion of a potentially life-threatening overdose.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

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

Mechanism of action (MOA)

Voltaren 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 an important role in causing inflammation, pain and fever.

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

Pharmacodynamics (PD)

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterized by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

In post-traumatic and post-operative inflammatory conditions, diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound edema.

In clinical trials Voltaren has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. Clinical studies have also revealed that, in primary dysmenorrhoea, Voltaren is capable of relieving the pain and reducing the extent of bleeding.

Pharmacokinetics (PK)

Absorption

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 micrograms/mL (5 micromol/L) are attained on average 2 hours after ingestion of one tablet of 50 mg.

The passage of a tablet through the stomach is slower when ingested with or after a meal than when it is taken before a meal, but the amount of diclofenac absorbed remains the same.

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.

The plasma concentrations attained in children given equivalent doses (mg/kg body weight) are similar to those obtained in adults.

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

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/metabolism

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-,4'-hydroxy-,5-hydroxy-,4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much lesser 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.

Linearity/non-linearity

The amount absorbed is linearly related to the size of the dose.

Special populations

Geriatric patients

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

Renal impairment

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a

creatinine clearance of <10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

Hepatic impairment

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

NON-CLINICAL SAFETY DATA

No mutagenic effects could be demonstrated in various in vitro and in vivo experiments, and no carcinogenic potential was detected in long term studies in rats and mice.

For more information, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

PHARMACEUTICAL INFORMATION

Incompatibilities

Not applicable.

Storage

See folding box.

Voltaren gastro-resistant tablets should not be used after the date marked “EXP” on the pack.

Voltaren gastro-resistant tablets must be kept out of the reach and sight of children.

Instructions for use and handling

No special requirements.

Manufacturer:

See folding box.

Package Leaflet

® = registered trademark

Novartis Pharma AG, Basel, Switzerland