NOVARTIS

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

Cardiovascular Risk :
● NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk .

● Voltaren is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) Surgery .

Gastrointestinal Risk :
● NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

COMPOSITION AND PHARMACEUTICAL FORM
The active substance is sodium-[o-[(2,6-dichlorophenyl)-amino]-phenyl]-acetate (= diclofenac sodium).
One Voltaren ampoule of 3 mL contains 75 mg of diclofenac sodium.
For excipients, see section EXCIPIENTS.
Solution for injection.

INDICATIONS
Intramuscular injection
Treatment of:
● Exacerbations of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
● Acute attacks of gout.
● Renal colic and biliary colic.
● Post-traumatic and post-operative pain, inflammation and swelling.
● Severe migraine attacks.
Intravenous infusion
Treatment or prevention of post-operative pain in a hospital setting.

DOSAGE AND ADMINISTRATION
As a general recommendation, the dose should be individually adjusted and the lowest effective dose given for the shortest possible duration.

Adults
Voltaren solution for injection should not be given for more than 2 days; if necessary, treatment can be continued with Voltaren tablets or suppositories.
Intramuscular injection
The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site.
The dose is generally one 75 mg ampoule daily, given by deep intragluteal injection into the upper outer quadrant. In severe cases (e.g. colic), the daily dose can exceptionally be increased to two injections of 75 mg, separated by an interval of a few hours (one into each buttock). Alternatively, one ampoule of 75 mg can be combined with other pharmaceutical forms of Voltaren (e.g. tablets, suppositories) up to a total maximum daily dose of 150 mg.
In migraine attacks, clinical experience is limited to initial use of one ampoule of 75 mg administered as soon as possible, followed by suppositories up to 100 mg on the same day if required. The total dose should not exceed 175 mg on the first day.

Intravenous infusion
Voltaren solution for injection must not be given as an intravenous bolus injection.
Immediately before starting an intravenous infusion, Voltaren solution for injection must be diluted with saline 0.9% or glucose 5% infusion solution buffered with sodium bicarbonate according to the instructions given in section INSTRUCTIONS FOR USE AND HANDLING.
Two alternative dosage regimens of Voltaren solution for injection are recommended.
For the treatment of moderate to severe post-operative pain, 75 mg should be infused continuously over a period of 30 minutes to 2 hours. If necessary, treatment may be repeated after a few hours, but the dose should not exceed 150 mg within any period of 24 hours.
For the prevention of post-operative pain, a loading dose of 25 mg to 50 mg should be infused after surgery over 15 minutes to 1 hour, followed by a continuous infusion of about 5 mg per hour up to a maximum daily dose of 150 mg.

Children and adolescents
Because of their dosage strength, the ampoules of Voltaren solution for injection are not suitable for children and adolescents.
CONTRAINDICATIONS
● Known hypersensitivity to the active substance, sodium metabisulphite or any of the other excipients.
● Active gastric or intestinal ulcer, bleeding or perforation.
● Last trimester of pregnancy (see section PREGNANCY AND LACTATION).
● Severe hepatic renal and cardiac failure (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
● Like other non-steroidal anti-inflammatory drugs (NSAIDs), Voltaren is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings
Gastrointestinal bleeding ulceration or perforation, which can be fatal, have been reported with all NSAIDs 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 occur in patients receiving Voltaren, the medicinal product should be withdrawn.
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 UNDESIRABLE EFFECTS). 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 without earlier exposure to diclofenac.
The sodium metabisulphite in the solution for injection can also lead to isolated severe hypersensitivity reactions and bronchospasm.
Like other NSAIDs, Voltaren may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Precautions
General
The concomitant use of Voltaren with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.
Caution is indicated in the elderly on basic medical grounds. In particular it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Pre-existing asthma
In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore special precaution 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.
Special caution is recommended when Voltaren is used parenterally in patients with bronchial asthma because symptoms may be exacerbated.

Gastrointestinal effects
As with all NSAIDs, 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 UNDESIRABLE EFFECTS). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.
To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.
Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin, or other medicinal products 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 by exacerbated (see section UNDESIRABLE EFFECTS).

Hepatic 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, 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 without prodromal symptoms.
Caution is called for when using Voltaren in patients with hepatic porphyria, since it may trigger an attack.

Renal effects
As fluid retention and oedema have been reported in association with NSAID therapy, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion 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 normally followed by recovery to the pre-treatment state.

Haematological effects
During prolonged treatment with Voltaren, 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.

INTERACTIONS
The following interactions include those observed with Voltaren solution for injection and/or other pharmaceutical forms of 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. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated 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 and SSRIs may increase the risk of gastrointestinal bleeding (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.
Methotrexate: Caution is recommended when NSAIDs are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.
Ciclosporin: Diclofenac, like other NSAIDs may increase the nephrotoxicity of ciclosporin 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.
Quinolone antibacterials: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

PREGNANCY AND LACTATION
Pregnancy
The use of diclofenac in pregnant women has not been studied. Therefore, Voltaren should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweights the risk to the foetus. As with other NSAIDs, use during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus (see section CONTRAINDICATIONS). Animal studies have not shown any directly or indirectly harmful effects on

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pregnancy, embryonal/fetal development, parturition or postnatal development (see section PRECLINICAL SAFETY DATA).

Lactation
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 effect in the infant.

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Patients experiencing visual disturbances, dizziness, vertigo, somnolence, or other central nervous system disturbances while taking Voltaren should refrain from driving or using machines.

UNDESIRABLE EFFECTS
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports.
The following undesirable effects include those reported with Voltaren solution for injection and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Table 1

Infections and infestations
Very rare: Injection site abscess.
Blood and lymphatic system disorders
Very rare: Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders
Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare: Angioneurotic oedema (including face oedema).
Psychiatric disorders
Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders
Common: Headache, dizziness.
Rare: Somnolence.
Very rare: Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances , cerebrovascular accident.
Eye disorders
Very rare: Visual disturbances, vision blurred, diplopia.
Ear and labyrinth disorders
Common : Vertigo.
Very rare: Tinnitus, hearing impaired.
Cardiac disorders
Very rare: Palpitations, chest pain, cardiac failure, myocardial infarction.
Vascular disorders
Very rare: Hypertension, vasculitis.
Respiratory, thoracic and mediastinal **disorders**
Rare: Asthma (including dyspnoea).
Very rare: Pneumonitis.
Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation).
Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder diaphragm-like intestinal strictures, pancreatitis.
Hepatobiliary disorders
Common: Transaminases increased.
Rare: Hepatitis, jaundice, liver disorder.
Very rare: Fulminant hepatitis.
Skin and subcutaneous tissue disorders
Common: Rash.
Rare: Urticaria.
Very rare: Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders
Very rare: Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions
Common: Injection site reaction, injection site pain, injection site induration.
Rare: Oedema, injection site necrosis.

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

Therapeutic measures
Management of acute poisoning with NSAIDs essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.
Special measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to the high protein binding and extensive metabolism.

PHARMACODYNAMICS
Mechanism of action
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 to be fundamental to its mechanism of action. Prostaglandins play an important role in causing inflammation, pain and fever.
Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans.

Pharmacodynamic effects
In rheumatic diseases, the anti-inflammatory and analgesic properties of Voltaren elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.
Voltaren has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin, an effect which sets in within 15 to 30 minutes.
Voltaren has also been shown to have a beneficial effect in migraine attacks.
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.
When used concomitantly with opioids for the management of post-operative pain, Voltaren significantly reduces the need for opioids.
Voltaren ampoules are particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases, and of painful conditions due to inflammation of non-rheumatic origin.

PHARMACOKINETICS
Absorption
After administration of 75 mg diclofenac by intramuscular injection, absorption sets in immediately, and mean peak plasma concentrations of about 2.5 micrograms/mL (8 micromol/L) are reached after about 20 minutes. The amount absorbed is in linear proportion to the size of the dose.
When 75 mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.9 micrograms/mL (5.9 micromol/L). Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentrations proportional to the infusion rate after 3 to 4 hours. In contrast, plasma concentrations decline rapidly once peak levels have been reached following intramuscular injection or administration of gastro-resistant tablets or suppositories.
The area under the concentration curve (AUC) after intramuscular or intravenous administration is about twice as large as it is following oral or rectal administration, because about half the active substance is metabolised during its first passage through the liver ("first pass" effect) when administered via the oral or rectal routes.
Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distributio
99.7% of diclofenac binds to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 L/kg.
Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been reached. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma levels, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

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

Characteristics in 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.
In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of less than 10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects.
However, the metabolites are ultimately cleared through the bile.
In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.
PRECLINICAL SAFETY DATA
Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.
Diclofenac had no influence on the fertility of parent animals in rats. The prenatal, perinatal and postnatal development of the offspring was not affected.

EXCIPIENTS
Mannitol; sodium metabisulphite (E223); benzyl alcohol; propylene glycol; water for injection; sodium hydroxide; nitrogen, pure.
Pharmaceutical formulations may vary between countries.

INCOMPATIBILITIES
As a rule, Voltaren solution for injection should not be mixed with other injection solutions.
Infusion solutions of sodium chloride 0.9% or glucose 5% without sodium bicarbonate as an additive present a risk of supersaturation, possibly leading to formation of crystals or precipitates. Infusion solutions other than those recommended should not be used.

STORAGE
See folding box.
Voltaren solution for injection should not be used after the date marked "EXP" on the pack.

INSTRUCTIONS FOR USE AND HANDLING
To be injected either intramuscularly by deep intragluteal injection into the upper outer quadrant, or intravenously by slow infusion after dilution in accordance with the following instructions. Each ampoule is for single use only. The solution should be used immediately after opening. Any unused contents should be discarded.
Depending on the intended duration of infusion (see section DOSAGE AND ADMINISTRATION), mix 100 to 500 mL of isotonic saline (sodium chloride 0.9% solution) or glucose 5% solution buffered with sodium bicarbonate injectable solution (0.5 mL of 8.4% or 1 mL of 4.2% or a corresponding volume of a different concentration) taken from a freshly opened container; add the contents of one Voltaren ampoule to this solution. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.
Note: Voltaren solution for injection should be kept out of the reach and sight of children.

Manufacturer:
See folding box.

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Novartis Pharma AG, Basel, Switzerland