

VOLTAREN[®]

(diclofenac sodium)

75 mg/3 mL solution for injection

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VOLTAREN® 75mg/3mL solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is diclofenac sodium.

One Voltaren ampoule of 3 mL contains 75 mg of diclofenac sodium.

Excipient(s) with known effect

Sodium metabisulphite, Benzyl alcohol, Propylene glycol (E 1520)

Each 3ml ampoule also contains 120mg Benzyl alcohol and 2mg sodium metabisulphite (E223) and 600mg propylene glycol (E 1520).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection, concentrate for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Voltaren for Intramuscular injection use is indicated in treatment of

- Exacerbations of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondyloarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
- Acute attacks of gout.
- Renal colic and biliary colic.
- Symptomatic short-term treatment of post-traumatic and post-operative pain (POP), inflammation and swelling.
- Severe migraine attacks.

Voltaren for Intravenous infusion use is indicated in treatment or prevention of postoperative pain in a hospital setting.

4.2 Posology and method of administration

Posology

As a general recommendation, the dose should be individually adjusted. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

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 (see Method of administration).

Special Populations

Paediatric population

Voltaren solution for injection is not recommended for use in children below 18 years of age.

Elderly

No adjustment of the starting dose is generally required for elderly patients aged 65 years or above (see section 4.4 Special warnings and precautions for use). However, caution is indicated on basic medical grounds, especially for frail elderly patients or those with a low body weight (see section 4.4 Special warnings and precautions for use).

Congestive Heart Failure (NYHA-I) or significant cardiovascular risk factors

Patients with congestive heart failure (NYHA-I) or significant risk factors for cardiovascular events should be treated with Voltaren only after careful consideration and only at doses ≤ 100 mg daily if treated for more than 4 weeks (see section 4.4 Special warnings and precautions for use).

Renal impairment

Voltaren is contraindicated in patients with renal failure ($GFR < 15 \text{ mL/min./1.73m}^2$) (see section 4.3 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 4.4 Special warnings and precautions for use).

Hepatic impairment

Voltaren is contraindicated in patients with hepatic failure (see section 4.3 Contraindications).

No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose recommendations can be made. Caution is advised when administering Voltaren to patients with mild to moderate hepatic impairment (see section 4.4 Special warnings and precautions for use).

Method of administration

Intramuscular injection

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.

Precautions to be taken before handling or administering the medicinal product

The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site (which may result in muscle weakness, muscle paralysis, hypoaesthesia and embolia cutis medicamentosa (Nicolau syndrome).

Voltaren solution for injection is administered intramuscularly by deep intragluteal injection into the upper outer quadrant using aseptic technique.

Appropriate injection technique and length of the needle (considering the thickness of the patient's gluteal fat) should be used to avoid inadvertent subcutaneous administration of Voltaren injection.

Intravenous infusion

Voltaren solution for injection must not be given as an intravenous bolus injection. Voltaren solution for injection is administered intravenously by slow infusion after dilution in accordance with the following instructions.

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 6.6 (Special precautions for disposal and other 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.

4.3 Contraindications

- Known hypersensitivity to the active substance, sodium metabisulphite or any of the other excipients.
- Active gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Last trimester of pregnancy (see section 4.6 Pregnancy and lactation).
- Hepatic failure
- Renal failure (GFR<15mL/min./1.73m²)

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- 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 reaction) (see section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).
 - Established congestive heart failure (NYHA II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

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.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac

Diclofenac solution for injection must not be given to premature babies or neonates. Benzylalcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years of age.

The instructions for intramuscular injection should be strictly followed in order to avoid adverse events at the injection site, which may result in muscle weakness, muscle paralysis, hypoaesthesia, embolia cutis medicamentosa (Nicolau syndrome) and injection site necrosis.

Gastrointestinal effects

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has 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 Diclofenac, the treatment should be discontinued.

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

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 4.8 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 hemorrhage or perforation. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

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)/aspirin, 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 4.5 Interaction with other medicinal products and other forms of interaction).

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 4.8 Undesirable effects).

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.

Renal effects

As fluid retention and oedema 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 4.3 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.

Injection site reactions

Injection site reactions have been reported after the intramuscular administration of Voltaren solution for injection, including injection site necrosis and embolia cutis medicamentosa, also known as Nicolau Syndrome (particularly after inadvertent subcutaneous administration). Appropriate needle selection and injection technique should be followed during intramuscular administration of Voltaren solution for injection (see section 4.2 Posology and method of administration).

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and generalised bullous fixed drug eruption have been reported very rarely in association with the use of diclofenac (see 4.8 Undesirable effects). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. 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 case with diclofenac without earlier exposure to the drug.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy.

Patients with congestive heart failure (NYHA-I) and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration and only at doses $\leq 100\text{mg}$ daily when treatment continues for more than 4 weeks.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. 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 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 Voltaren, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, diclofenac 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.

Special caution is recommended when Voltaren is used parenterally in patients with bronchial asthma because symptoms may be exacerbated.

The instructions for intramuscular injection should be strictly followed in order to avoid adverse events at the injection site, which may result in muscle weakness, muscle paralysis, hypoaesthesia and injection site necrosis.

Geriatric patients

Caution is indicated in the elderly on basic medical grounds especially used 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 4.5 Interactions with other medicinal products and other forms of interactions).

Masking signs of infections

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

Special Excipients

The sodium metabisulphite present in solution for injection can also lead to isolated severe hypersensitivity reactions and bronchospasm.

Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates (“gasping syndrome”). The minimum amount of benzyl alcohol at which toxicity may occur is not known. High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis). Increased risk due to accumulation in young children.

The propylene glycol present when co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

This medicinal product contains less than 1 mmol sodium (23 mg) in 3 milliliter, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with Voltaren solution for injection 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 sulfapyrazone and 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 4.4 Special warnings and precaution for use).

Ciclosporin and tacrolimus: 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 and 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 4.4 Special warnings and precautions for use).

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 4.4 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 4.4 Special warnings and precautions for use). 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 4.4 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.

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: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. 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.

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

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).

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

There are no data to suggest any recommendations for women of child-bearing potential.

Pregnancy

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.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. During the first and second trimester of pregnancy, Voltaren should not be given unless clearly necessary. If Voltaren is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios is found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; (see above);
- the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Voltaren is contraindicated during the third trimester of pregnancy.

Breast-feeding

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, Voltaren should not be administered during breastfeeding 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.

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are 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 ($\geq 1/100, <1/10$); uncommon ($\geq 1/1,000, <1/100$); rare ($\geq 1/10,000, <1/1,000$); very rare ($<1/10,000$),not known: cannot be estimated from the available data.

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.
Not known	Injection site necrosis
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:	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, hearing impaired.
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, melana, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis or perforation, which may lead to peritonitis).
Very rare:	Colitis (including haemorrhagic colitis, ischaemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, esophageal disorder, intestinal diaphragm disease, pancreatitis.
Not known	Ischemic colitis
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.
Not known:	Fixed drug eruption, Generalised bullous fixed drug eruption

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

Common: Injection site reaction, injection site pain, injection site induration.

Rare: Edema, injection site necrosis.

Not known: Embolia cutis medicamentosa (Nicolau syndrome)

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

Description of selected adverse drug reactions**Arteriothrombotic events**

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment (see section 4.3 and 4.4 for Contraindications and Special Warnings and precautions for use).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose**Symptoms**

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

There is limited clinical trial experience of the use of diclofenac in juvenile rheumatoid arthritis (JRA) paediatric patients. In a randomised, double blind, 2-week, parallel group study in children aged 3-15 years with JRA/(juvenile idiopathic arthritis (JIA), the efficacy and safety of daily 2-3mg/kg BW diclofenac was compared with acetylsalicylic acid (ASS, 50-100mg/kg BW/d) and placebo- 15 patients in each group. In the global evaluation, 11 of 15 diclofenac patients, 6 of 12 aspirin and 4 of 15 placebo patients showed improvement with the difference being statistically significant ($p < 0.05$). The number of tender joints decreased with diclofenac and ASS but increased with placebo. In a second randomised, double-blind, 6-week, parallel group study in children aged 4-15 years with JRA/JIA, the efficacy of diclofenac (daily dose 2-3mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3 mg/kg BW, n=23)

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 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.

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 edema.

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.

5.2 Pharmacokinetic properties

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. 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 metabolized 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.

Distribution

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.

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

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 \pm 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 in linear proportion to the size of the dose.

Special populations

Elderly: 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 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.

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.

Voltaren is a well-established product.

5.3 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. In standard preclinical animal studies, 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. Except for minimal fetal effects at maternally toxic doses, the prenatal, perinatal and postnatal development of the offspring was not affected.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat and led to premature closure of the ductus arteriosus in the pregnant rat. 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 constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors (see sections 4.3 Contraindications and 4.6 pregnancy, breast-feeding and fertility).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol; sodium metabisulphite (E223); benzyl alcohol; propylene glycol; water for injection; sodium hydroxide; nitrogen.

6.2 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.

6.3 Shelf life

2 years.

Intravenous infusions should be initiated immediately after preparing the infusion solutions (see section 6.6 Instructions for use/handling). The infusion solutions should not be stored.

6.4 Special precautions for storage

Protect from light and heat (Store below 30°C).

Medicines should be kept out of the reach and sight of children.

6.5 Nature and contents of container

Colourless glass ampoules of 3 ml.

Pack size/s: 5, 10 ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Depending on the intended duration of infusion (see section 4.2 Posology and method of administration), mix 100 to 500 mL of isotonic saline (sodium chloride 0.9% solution) or glucose 5% solution with the contents of one Voltaren ampoule. Both solutions should be 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. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.

Each ampoule is for single use only. The solution should be used immediately after opening. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKET AUTHORISATION HOLDER

Novartis Ireland Limited
Vista Building,
Elm Park, Merrion Road,
Ballsbridge, Dublin 4,
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8. MARKET AUTHORISATION NUMBER(S)

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