1 PRODUCT NAME

VOLTAREN® 75 mg/3 mL Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 3 mL contains 75 mg of diclofenac sodium.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Intramuscular injection

Treatment of:

- Renal colic and biliary colic.
- Severe migraine attacks when other forms of Voltaren are considered unsuitable.

Intramuscular injection

Treatment or prevention of post-operative pain in a hospital setting.

4.2 Dose and method of administration

Voltaren should only be prescribed when the benefits are considered to outweigh the potential risks. After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Dosage

General population

Voltaren solution for injection should not be given for more than 2 days; if necessary, treatment can be continued with Voltaren tablets or suppositories.

Special populations

Paediatric population

Because of their dosage strength, the ampoules of Voltaren solution for injection are not suitable for children and adolescents.

Geriatric population (Patients aged 65 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 (see section 4.4).

Patients with established cardiovascular disease or significant cardiovascular risk factors
Treatment with Voltaren solution for injection is generally not recommended in patients with established cardiovascular disease or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease

should be treated with Voltaren solution for injection only after careful consideration and only at doses ≤100 mg daily initial treatment with Voltaren solution for injection continues e.g. with Voltaren tablets or suppositories for more than 4 weeks (see section 4.4).

Patients with renal impairment
Voltaren is contraindicated in patients with renal failure (see section 4.3).

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).

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

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 section 4.4).

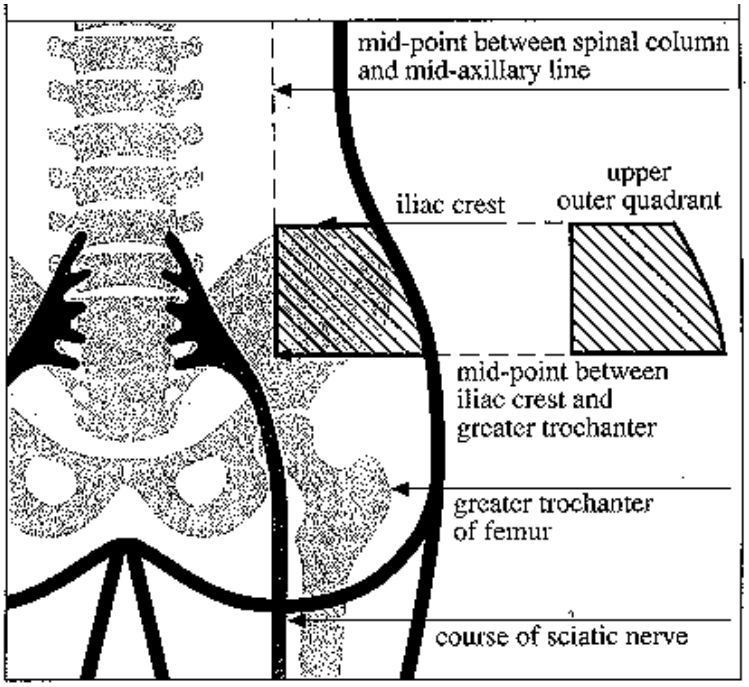
Method of Administration

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 (which may result in muscle weakness, muscle paralysis, hypoaesthesia and Embolia cutis medicamentosa (Nicolau syndrome)).

The dose is generally one 75 mg ampoule daily, given by deep intragluteal injection into the upper outer quadrant using aseptic technique. 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 6.6.

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 to any of the excipients (see section 6.1).
- Active gastric or intestinal ulcer, bleeding or perforation.
- Last trimester of pregnancy (see section 4.6).
- Hepatic failure.
- Renal failure (GFR <15 mL/min/1.73m^2).
- Severe cardiac failure (see section 4.4).
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Voltaren is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

4.4 Special warnings and precautions for use

General

Patients on long-term treatment should be reviewed regularly with regards to efficacy, adverse effects, the development of risk factors and the on-going need for therapy. Consideration should be given to monitoring blood pressure, haemoglobin levels and renal function.

Cardiovascular thrombotic events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk.

Patients with previous myocardial infarction (within the last 6 to 12 months) should not use diclofenac. Treatment with Voltaren is generally not recommended in patients with established cardiovascular disease (e.g. congestive heart failure, established ischaemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking) should be treated with Voltaren only after careful consideration and only at doses ≤100 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 lowest effective daily dose should be used for the shortest duration possible (see section 4.2). The patient's need for symptomatic relief and response to therapy should be reevaluated periodically, especially when treatment continues for more than 4 weeks.

Prescribers should inform the individual patient of the possible increased risk when prescribing diclofenac for patients at high risk of cardiovascular events.

Physicians and patients should remain alert for such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of cardiovascular toxicity and the steps to take should they occur. 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 warning. Patients should be instructed to see a physician immediately in case of such an event.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs, therefore caution is advised in patients with fluid retention or heart failure.

Gastrointestinal effects

Gastrointestinal bleeding, ulceration or perforation, which may increase with dose or duration of use and 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 occur in patients receiving Voltaren, the treatment should be discontinued.

Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism.

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). 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 4.5).

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).

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

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.

Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

Severe skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia with SystemicSymptoms (DRESS) (see Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)), have been reported very rarely in association with the use of NSAIDs, including Voltaren (see section 4.8). These serious adverse events are idiosyncratic and are independent of dose or duration of use. 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. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity, and Voltaren should be discontinued.

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

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

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

DRESS syndrome has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS syndrome typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS syndrome may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue the NSAID and evaluate the patient immediately.

Masking signs of infections

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

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.

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, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Voltaren, 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 from any cause, e.g. before or after major surgery (see section 4.3). 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.

Injection site reactions

Injection site reactions have been reported after the administration of Voltaren intramuscularly, 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 i.m. administration of Voltaren (see section 6.7 Special precautions for disposal and handling)

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.

Geriatric patients

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 (see section 4.2).

Interactions with other NSAIDs

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 (see section 4.5).

4.5 Interaction with other medicines 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 potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

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).

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).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4). 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).

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.

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.

Cyclosporin and Tacrolimus: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of cyclosporin 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 cyclosporin 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)

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

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

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

Use in 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 should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the foetus.

In addition, Voltaren should not be used during the third trimester of pregnancy (see section 4.3).

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 4.3).

Human data

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

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. 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.

Human data

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.

Labour or Delivery

There are no studies on the effects of Voltaren during labour 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 4.3).

Breastfeeding

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.

Fertility

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.

4.7 Effects on ability to drive and use machines

Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness, or fatigue while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects

Adverse drug reactions from clinical trials and/or spontaneous or literature reports (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 (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

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. Adverse drug reactions

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:	Angioedema (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, meningitis aseptic, 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 unknown:	Kounis syndrome
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, melaena, haemorrhagic diarrhoea, gastrointestinal ulcer (with or without bleeding gastrointestinal stenosis or perforation which may lead to peritonitis).
Very rare:	Colitis (including haemorrhagic colitis, ischemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, intestinal diaphragm disease, pancreatitis, haemorrhoids aggravated.
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, allergic purpura, Henoch-Schonlein purpura, pruritus.
Unknown	Drug reaction with eosinophilia with systemic symptoms (DRESS)
Renal and urinary disorders	
Very rare:	Acute kidney injury (acute renal failure), haematuria, 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:	Oedema, injection site necrosis

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

Adverse drug reactions from post-marketing experience (frequency not known)

The following adverse drug reaction has been derived from post-marketing experience with Voltaren. Because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency which is therefore categorized as not known.

Table 2 Adverse drug reaction derived from post-marketing experience (frequency not known)

Injection site reactions
Embolia cutis medicamentosa (Nicolau syndrome)

Description of selected adverse 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 4.4).

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 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, 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 haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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).

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 fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain, and fever.

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

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 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.

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.

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.

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 smaller 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 in linear proportion to the size of the dose.

Pharmacokinetics in special patient groups

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 <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.

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.

Oligohydramnios/Fetal Renal Impairment

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.

Labour or Delivery

In animal studies, NSAIDS, including diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Information might differ in some countries.

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.

6.4 Special precautions for storage

Store below 30°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Colourless glass ampoules of 3 mL in packs of 5.

6.6 Special precautions for disposal and handling

The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site.

To be injected either intramuscularly by deep intragluteal injection into the upper outer quadrant using aseptic technique, 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.

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.

Depending on the intended duration of infusion (see Dosage of 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.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4 Special warnings and precautions for use	Added text about Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)
4.8 Adverse effects	Added DRESS to Table 1 Adverse drug reactions

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