NOVARTIS

VOLTAREN® 25, VOLTAREN® GT 50, VOLTAREN® 75, VOLTAREN® SR 100 TABLETS

VOLTAREN® 75 AMPOULES

VOLTAREN® 25 SUPPOSITORIES, VOLTAREN® 100 SUPPOSITORIES

PROFESSIONAL INFORMATION

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1. NAME OF THE MEDICINE

VOLTAREN® 25 TABLETS

VOLTAREN® GT 50 TABLETS

VOLTAREN® 75 TABLETS

VOLTAREN® SIMPLE REGIMEN 100 TABLETS

VOLTAREN® 75 AMPOULES

VOLTAREN® 25 SUPPOSITORIES

VOLTAREN® 100 SUPPOSITORIES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is sodium-[o[(2,6-dichlorophenyl)-amino]-phenyl]-acetate (= diclofenac sodium).

One enteric-coated tablet contains 25 mg diclofenac sodium.

Contains sugar: 16 mg lactose monohydrate

One enteric-coated tablet contains 50 mg diclofenac sodium.

Contains sugar: 25 mg lactose monohydrate

One film-coated tablet contains 75 mg diclofenac sodium.

Contains sugar: 90,8 mg sucrose

One film-coated tablet contains 100 mg diclofenac sodium.

Contains sugar: 119 mg sucrose

One 75 mg/3 mL ampoule contains 75 mg diclofenac sodium

Excipients with known effect:

Contains sugar: 18 mg mannitol

Preservative: benzyl alcohol 4 % mass/volume

Antioxidant: sodium metabisulphite 0,067 % mass/volume

Voltaren Ampoules contains 600 mg propylene glycol.

One suppository contains 25 mg and 100 mg diclofenac sodium

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

VOLTAREN 25:

Yellow, round, slightly biconvex, enteric-coated tablet with bevelled edges. Printed one side CG and the other side BZ.

VOLTAREN GT 50:

Light brown, round, slightly biconvex, enteric-coated tablet with bevelled edges. Printed one side CG and the other side GT.

VOLTAREN 75 TABLETS:

Pale pink, triangular, slightly biconvex, film coated tablets. Printed CG or Geigy on one side and ID on the other, or no printing on either side.

VOLTAREN SIMPLE REGIMEN 100:

Pink, round, film coated, slightly biconvex with bevelled edges. Printed one side CG and the other side CGC.

VOLTAREN 75 AMPOULES:

Clear, colourless to faintly yellowi solution contained in clear, glass, labelled ampoules.

VOLTAREN 25 SUPPOSITORIES:

Yellowish-white, torpedo shaped, approximately 1 g in mass.

VOLTAREN 100 SUPPOSITORIES:

Yellowish-white, torpedo shaped, approximately 2 g in mass.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthrosis and spondylarthritis.

Painful musculoskeletal conditions.

Non-articular rheumatism.

Acute attacks of gout.

Mild to moderately painful post-operative and post-traumatic inflammation and swelling, pain following dental surgery or orthopaedic surgery.

Symptomatic treatment of primary dysmenorrhoea.

Migraine attacks.

VOLTAREN 75 AMPOULES used for Intramuscular injection

For initial therapy for inflammatory and degenerative rheumatic diseases, as well as for the treatment of mild to moderately painful conditions due to inflammation of non-rheumatic origin.

VOLTAREN 75 AMPOULES used for the preparation of Intravenous infusion

Treatment or prevention of post-operative mild to moderate pain of inflammatory origin in the absence of any infection.

4.2 Posology and method of administration

Because of their dosage strength, the following dosage strengths are not suitable for use in children and adolescents below 14 years of age; VOLTAREN 25 tablets could be used in these patients.

● VOLTAREN GT 50 TABLETS

● VOLTAREN 75 TABLETS

● VOLTAREN SIMPLE REGIMEN 100 TABLETS

● VOLTAREN 75 AMPOULES

● VOLTAREN 100 SUPPOSITORIES

Adults

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

VOLTAREN 25; VOLTAREN GT 50

The tablets should be swallowed whole with a glass of water and must not be divided or chewed. For the relief of acute pain, the tablets should preferably be taken on an empty stomach.

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

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

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

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

Geriatrics (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 patients with a low body weight. (see section 4.4)

VOLTAREN 75 TABLETS and VOLTAREN SIMPLE REGIMEN 100 TABLETS

As a rule, the initial daily dosage is 100 mg to 150 mg administered as 1 tablet of VOLTAREN SIMPLE REGIMEN 100 as a single dose or as 2 tablets of VOLTAREN 75 TABLETS taken in two divided doses.

In milder cases, as well as for long-term therapy, 1 tablet of VOLTAREN 75 TABLETS daily is usually sufficient.

The VOLTAREN 75 TABLETS and VOLTAREN SIMPLE REGIMEN 100 tablets should neither be fragmented nor chewed and should preferably be taken at mealtimes. Where the symptoms are most pronounced during the night or in the morning.

VOLTAREN SIMPLE REGIMEN 100 tablets should preferably be taken in the evening.

VOLTAREN 75 AMPOULES should not be given for more than two days; if necessary, the 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.

Only for deep intragluteal injection into the upper outer quadrant.

After inserting the needle, the plunger should be pulled back to avoid inadvertent intra-arterial injection.

For adults the dose is generally one VOLTAREN 75 AMPOULE daily. VOLTAREN 75 AMPOULES should not be mixed with other injection solutions.

By way of exception, in severe cases, two injections of 75 mg, separated by an interval of a few hours, can be given per day (one into each buttock).

Alternatively, it is possible to combine one ampoule of 75 mg with either VOLTAREN 25 or VOLTAREN GT 50 tablets up to a maximum daily dosage of 150 mg.

VOLTAREN 75 AMPOULES used for the preparation of intravenous infusion.

VOLTAREN 75 AMPOULES must not be given as an intravenous bolus injection and must 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. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.

Do not use infusion solutions other than those recommended.

To prepare an intravenous infusion, one VOLTAREN 75 AMPOULE should be diluted with 100 mL – 500 mL of either sodium chloride solution (0,9 %) or glucose solution (5 %). Both solutions should first be buffered with bicarbonate solution (0,5 mL 8,4 % or 1 mL 4,2 %). Only clear infusion solutions should be used. VOLTAREN infusions should be freshly made up and used immediately. Once prepared, the infusion should not be stored. VOLTAREN should not be administered as an intravenous bolus injection.

Two alternative dosage regimens of VOLTAREN IV Infusion are recommended

• For the treatment of moderate to severe postoperative pain, 75 mg should be infused continuously over a period of 30 minutes to 2 hours. If necessary, treatment may be repeated, but a total dosage of 150 mg within any period of 24 hours must not be exceeded.

• For the prevention of postoperative 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 approximately 5 mg per hour up to a maximum daily dosage of 150 mg.

VOLTAREN infusion should not be given for more than 2 days; if necessary, treatment to be continued with tablets or suppositories.

VOLTAREN 25 SUPPOSITORIES

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

VOLTAREN 100 SUPPOSITORIES

The average adult dose is one VOLTAREN 100 SUPPOSITORIES daily.

To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of one VOLTAREN 100 SUPPOSITORIES at bedtime, up to a maximum dosage of 150 mg daily.

Note:

Not to be taken by mouth, as per rectal use only. The suppositories should be inserted well into the rectum. It is recommended to take the suppositories after passing stools.

Suppositories should never be divided for administration as incorrect storage conditions could have led to an uneven distribution of active substance in the suppository.

Do not use suppositories deformed by exposure to temperatures above 30 °C.

4.3 Contraindications

- History of gastrointestinal perforation, ulceration, or bleeding. Active or history of recurrent ulcer/haemorrhage/perforations
- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with porphyria.
- Last trimester of pregnancy and during lactation due to the risk of oligohydramnios/ foetal renal dysfunction (see section 4.6).
- Hepatic failure
- Renal failure (GFR <15 MLml/MINmin/1.73m^2)
- Severe cardiac failure
- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Patients in whom the use of acetylsalicylic acid or other NSAIDs can precipitate asthma, angioedema, urticaria, or acute rhinitis (i.e. NSAID-induced cross-reactivity reactions)
- Children under the age of two years.

VOLTAREN 75 AMPOULES

- The intravenous use in children is contraindicated due to insufficient evidence.
- Known sensitivity to sodium metabisulphite.
- NB: The intravenous use of VOLTAREN 75 AMPOULES is absolutely contraindicated in patients with impaired renal function and/or any form of shock.

VOLTAREN 25 SUPPOSITORIES and VOLTAREN 100 SUPPOSITORIES

- Proctitis

4.4 Special warnings and precautions for use

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

As with all NSAIDs, including diclofenac, close medical surveillance is imperative, and particular caution should be exercised when prescribing VOLTAREN in patients with symptoms indicative of gastrointestinal disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. 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 medicines (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of low-dose acetylsalicylic acid (ASA) or other drugs likely to increase gastrointestinal risk.

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

Close medical surveillance and caution should be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated.

When gastrointestinal bleeding or ulceration occurs in patients receiving VOLTAREN, treatment with VOLTAREN should be stopped.

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

Cardiovascular and cerebrovascular effects:

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

Treatment with VOLTAREN is generally not recommended in patients with established cardiovascular disease (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, hyperlipidaemia,

diabetes mellitus and smoking) should be treated with VOLTAREN only after careful consideration and only at doses ≤ 100 mg daily when treatment continues form more than 4 weeks.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patients 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 medical practitioner immediately in case of such an event.

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with VOLTAREN therapy. In view of VOLTAREN's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Haematological 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, bleeding diathesis or haematological abnormalities 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 disease 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 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.

Like other medicines that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

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Special caution is recommended when used parenterally especially in patients with bronchial asthma because symptoms may be exacerbated. The presence of sodium metabisulphite can, lead to isolated hypersensitivity reactions, which may manifest as an acute asthma attack, clouding of consciousness, or shock.

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, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, or 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 the use of diclofenac without prodromal symptoms.

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

Skin reactions:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with VOLTAREN (see sections 4.4 and 4.8). 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.

Allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases without earlier exposure to diclofenac.

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.

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.

Interactions with other NSAIDs

The concomitant use of VOLTAREN with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the potential for additive undesirable effects. (see section 4.5).

VOLTAREN may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Note:

VOLTAREN 25 and VOLTAREN GT 50 contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

VOLTAREN 75 mg and VOLTAREN SR 100 tablets contain sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take VOLTAREN 75 mg and VOLTAREN SR 100 tablets

VOLTAREN 75 mg and VOLTAREN SR 100 tablets contain sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

The following interactions include those observed with VOLTAREN tablets and/or other pharmaceutical forms of diclofenac.

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

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

Diuretics and antihypertensive agents: Concomitant use of VOLTAREN with diuretics or antihypertensive medicines (e.g. beta-adrenoceptor 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).

Medicines known to cause hyperkalaemia: Concomitant use of VOLTAREN with potassium sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should be monitored frequently (see section 4.4).

Other NSAIDs and corticosteroids: Concomitant administration of VOLTAREN and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4).

Anticoagulants and anti-platelet medicines: The bioavailability of VOLTAREN is reduced by acetylsalicylic acid, and that of acetylsalicylic acid by VOLTAREN, when the two products are administered together. Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4).

There are reports of an increased risk of haemorrhage in patients receiving VOLTAREN 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 4.4).

Antidiabetics: There have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic medicines during treatment with VOLTAREN. 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 renal impairment.

Methotrexate: Caution is recommended when VOLTAREN is 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 and tacrolimus: VOLTAREN may increase the nephrotoxicity of ciclosporin and tacrolimus due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin or tacrolimus.

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

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

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

4.6 Fertility, pregnancy, and lactation

Pregnancy

Use during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia, foetal renal impairment with subsequent oligohydramnios/ foetal renal dysfunction and/or premature closure of the ductus arteriosus and pulmonary hypertension (see section 4.3).

Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis, in some cases.

The onset of labour may be delayed, and its duration increased.

Lactation

VOLTAREN 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 (see section 4.3).

Fertility

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

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking VOLTAREN, should refrain from driving or using machines.

4.8 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 tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Administration of the suppositories may give rise to systemic side-effects. Suppositories may cause exacerbation of haemorrhoids.

Table 1
Injections and infestations
Very rare: Injection site abscess
Blood and lymphatic system disorders
Very rare: Thrombocytopenia, leucopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis

Immune system disorders

Rare: Hypersensitivity reactions, 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: Disturbances of sensation, paraesthesia, memory *impairment*, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

Eye disorders

Very rare: Visual impairment, blurred vision, diplopia

Ear and labyrinth disorders

Common: Vertigo.

Very rare: Tinnitus, impaired hearing.

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, decreased appetite.

Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, haemorrhagic diarrhoea, melaena, gastro-intestinal ulcer (with or without bleeding 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, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.

Hepatobiliary disorders

Common: Transaminases increased (SGOT, SGPT).

Rare: Hepatitis, jaundice, liver disorder.

Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure

Skin and subcutaneous tissue disorders

Common: Rash.

Rare: Urticaria.

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

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 reactions, injection site pain, injection site induration,

application site irritation (suppositories)

Rare : Oedema

Selected adverse drug reactions:

Arteriothrombotic events:

Meta-analysis and pharmacoepidemiological data point to 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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Novartis adverse drug reaction reporting:

Web: www.novartis.com/report

Email: patientsafety.sacg@novartis.com

Tel: +27 11 347 6600

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from VOLTAREN overdosage. Overdosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal haemorrhage, diarrhoea, dizziness, disorientation, excitation, tinnitus or convulsions and coma. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures

Management of acute poisoning with VOLTAREN 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 VOLTAREN due to the high protein binding and extensive metabolism.

Activated charcoal may be considered within one hour after ingestion of a potentially toxic overdose.

5. PHARMACOLOGICAL PROPERTIES

A 3.1 Antirheumatics (anti-inflammatory agents)

5.1 Pharmacodynamic properties

Diclofenac is a non-steroidal compound with antirheumatic, anti-inflammatory, analgesic and antipyretic properties. In vitro its active substance strongly inhibits prostaglandin-synthetase and also has an inhibitory effect on platelet aggregation.

Inhibition of prostaglandin biosynthesis, which has been demonstrated experimentally, is regarded as having an important bearing on its mechanism of action. Prostaglandins play a major role in the pathophysiology of inflammation, pain and fever.

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

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

VOLTAREN 75 AMPOULES, have 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.

5.2 Pharmacokinetic properties

Absorption

VOLTAREN 25; VOLTAREN GT 50

Diclofenac is absorbed after passage through the stomach.

Following ingestion of one tablet on an empty stomach, absorption occurs more rapidly than when the tablet is taken during or after a meal, but bioavailability remains the same.

The plasma concentrations show a linear relationship to the size of the dose. Peak levels are attained in 1 to 4 hours with the tablets and in the case of the suppositories in less than 1 hour.

VOLTAREN 75 TABLETS and VOLTAREN SIMPLE REGIMEN 100

The systematic availability of diclofenac from VOLTAREN 75 TABLETS and VOLTAREN SIMPLE REGIMEN 100 is on average 82 % of that achieved with same dose of VOLTAREN administered in the form of gastro-resistant tablets (possibly due to release-rate dependent “first-pass” metabolism)

As a result of a slower release of the active substance from VOLTAREN 75 TABLETS and VOLTAREN SIMPLE REGIMEN 100, peak concentrations attained are lower than those observed following the administration of gastro-resistant tablet.

Mean peak plasma concentrations of 0,5 µg/mL or 0,4 µg/mL (1,6 µmol or 1,25 µmol/l) are reached on average 4 hours after ingestion of prolonged release tablet of 100 mg or 75 mg. Mean plasma concentrations of 13 ng/ml (40nmol/l) can be recorded at 24 hours (16 hours) after administration of Voltaren prolonged-release 100 mg (75 mg) tablets.

Since half of diclofenac is metabolised during its first passage through the liver (“first pass” effect), the area under the concentration curve (AUC) following oral or rectal administration is about half that following an equivalent parenteral dose.

The peak plasma concentration, though comparable with that reached after a single coated tablet of 25 mg, is maintained over a longer period due to the larger quantity of diclofenac contained in VOLTAREN 75 TABLETS and VOLTAREN SIMPLE REGIMEN 100.

VOLTAREN 75 AMPOULES

After administration of 75 mg diclofenac by intramuscular injection, absorption sets in immediately and mean peak plasma concentrations of about 2.5 µg/ml (or 8 µmol/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 µg/ml (5,9 µmol/l)

Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentration 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.

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 of the active substance is metabolised during its first passage through the liver (“first pass” effect) when administered via the oral or rectal routes.

VOLTAREN 25 mg and 100 mg Suppositories

Diclofenac shows a rapid onset of absorption from suppositories, although the rate of absorption is slower than from gastro-resistant tablets administered orally. After administration of 50 mg suppositories, the peak plasma concentrations are attained on average within 1 hour, but maximum concentrations per dose unit are about two thirds of those reached after administration of gastro resistant tablets.

Since half of diclofenac is metabolised during its first passage through the liver (“first pass” effect), the area under the concentration curve (AUC) following oral or rectal administration is about half that following an equivalent parenteral dose.

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

For all formulations, the 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.

Metabolism:

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

Two of these phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination:

Total systemic clearance of diclofenac from plasma is 263 ± 56 mL/min (mean value ± SD). The total terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the 2 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 glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1 % excreted as unchanged substance.

The rest of the dose is eliminated as metabolites through the bile in the faeces.

Special Populations:

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Voltaren 25: colloidal anhydrous silica, lactose (16 mg), maize starch, sodium starch glycollate, povidone, microcrystalline cellulose, magnesium stearate (1 mg); hypromellose, yellow iron oxide (E 172), purified

talc, titanium dioxide (E 171), methacrylic acid copolymer, polyethylene glycol 8000, simeticone, polyoxyethylene 40 hydrogenated castor oil.

Voltaren GT 50: colloidal anhydrous silica, lactose (25 mg), maize starch, sodium starch glycollate povidone, microcrystalline cellulose, magnesium stearate (1,5 mg); hypromellose, yellow iron oxide (E 172), purified talc, titanium dioxide (E 171), methacrylic acid - copolymer, polyethylene glycol 8000, simeticone, red iron oxide (E 172), polyoxyethylene 40 hydrogenated castor oil.

Voltaren 75: colloidal anhydrous silica, sucrose, cetyl alcohol, povidone, magnesium stearate.; hypromellose, purified talc, polysorbate 80, titanium dioxide (E 171), red iron oxide (E172), polyethylene glycol 8000, printing ink: Black (Opacode S-1-8015), shellac; medicinal charcoal.

Voltaren SIMPLE REGIMEN SR 100: colloidal anhydrous silica, sucrose, cetyl alcohol, povidone, magnesium stearate.; hypromellose, purified talc, polysorbate 80, titanium dioxide (E 171), red iron oxide (E172), polyethylene glycol 8000, printing ink: Black (Opacode S-1-8015), shellac; medicinal charcoal.

VOLTAREN AMPOULES: mannitol; sodium metabisulphite (E223); benzyl alcohol; propylene glycol; water for injection; sodium hydroxide; nitrogen (pure).

VOLTAREN SUPPOSITORIES: Hard fat

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Voltaren 25 mg and Voltaren GT 50: 24 months

Voltaren 75 mg and Voltaren SIMPLE REGIMEN 100 mg: 36 months

Voltaren 75 mg ampoules: 24 months

Voltaren 25 suppositories and Voltaren 100 mg Suppositories: 36 months

6.4 Special precautions for storage

VOLTAREN 25; VOLTAREN GT 50:

Store below 30 °C.

Protect from moisture.

VOLTAREN 75 TABLETS:

Store below 30 °C.

Protect from moisture.

VOLTAREN SIMPLE REGIMEN 100:

Store below 30 °C.

Protect from moisture.

VOLTAREN 75 AMPOULES:

Store below 30 °C.

Store in the original package in order to protect from light.

VOLTAREN 25 SUPPOSITORIES and VOLTAREN 100 SUPPOSITORIES:

Store below 30 °C at all times.

6.5 Nature and contents of container

VOLTAREN 25 is supplied as enteric-coated tablets of 25 mg in packs of 30 and 50.

VOLTAREN GT 50 is supplied as enteric-coated tablets of 50 mg in blister packs of 15 and 20.

VOLTAREN 75 TABLETS are supplied in packs of 10 and 30.

VOLTAREN SIMPLE REGIMEN 100 tablets are supplied in blister packs of 28 and 30.

VOLTAREN 75 AMPOULES: 75 mg/3 mL in packs of 5, 50 and 200.

VOLTAREN 25 SUPPOSITORIES and VOLTAREN 100 SUPPOSITORIES are supplied in packs of 5.

6.6 Special precautions for disposal other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

NOVARTIS SOUTH AFRICA (PTY) LTD

Magwa Crescent West,

Waterfall City,

Jukskei view,

Johannesburg,

2090

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8. REGISTRATION NUMBERS

VOLTAREN 25 (enteric coated): G/3.1/83

VOLTAREN GT 50 (enteric coated): K/3.1/253

VOLTAREN 75 TABLETS: Y/3.1/346

VOLTAREN SIMPLE REGIMEN 100: M/3.1/63

VOLTAREN 75 AMPOULES: H/3.1/34

VOLTAREN 25 SUPPOSITORIES: R/3.1/224

VOLTAREN 100 SUPPOSITORIES: L/3.1/126

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

November 2007

10. DATE OF REVISION OF THE TEXT

20 May 2025

2008-PSB/GLC-0151-s, 2010-PSB/GLC-0265-s, 2011-PSB/GLC-0499-s, 2013-PSB/GLC-0631-s, 2015-PSB/GLC-0778-s, 2017-PSB/GLC-0907-s, 2019-PSB/GLC-1052-s