NOVARTIS

VOLTAREN®

(diclofenac sodium)

Enteric-coated tablet
Prolonged-release tablet

Product Information

DISETUJUI OLEH BPOM : 17/10/2024

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Cardiovascular risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This may increase with dose and duration of use. Voltaren is contraindicated in established congestive heart failure (New York Heart Association [NYHA] classification II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. Patients with congestive heart failure (NYHA-I) or risk factors for cardiovascular disease may be at greater risk (see section 6 Warnings and precautions).
- Voltaren is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see section 6 Warnings and precautions).

Gastrointestinal risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see section 6 Warnings and precautions).

1 Tradenames

VOLTAREN® (25 mg enteric-coated tablets)

VOLTAREN® (50 mg enteric-coated tablets)

VOLTAREN® SR 75 (75 mg prolonged-release tablets)

VOLTAREN® RETARD (100 mg prolonged-release tablets)

2 Description and composition

Pharmaceutical form(s)

Enteric-coated tablets (gastro-resistant tablets)

Film-coated tablets (prolonged-release tablets)

Active substance(s)

The active substance is diclofenac sodium.

Enteric coated tablet

One enteric-coated tablet contains 25 mg or 50 mg diclofenac sodium.

Prolonged-release tablet

One prolonged-release tablet contains 75 or 100 mg diclofenac sodium.

Active moiety

Diclofenac

Excipients

Enteric coated tablet

Core: microcrystalline cellulose, lactose monohydrate, magnesium stearate, maize (corn) starch, polyvinylpyrrolidone, silicone dioxide, sodium carboxymethyl starch (sodium starch glycolate), purified water.

Coating: hydroxypropyl methylcellulose, iron oxide red*, iron oxide yellow, polyoxyl 40 hydrogenated castor oil, methacrylic acid – ethyl acrylate copolymer, polyethylene glycol 8000, talc, titanium dioxide, silicon antifoam emulsion (dimeticone), purified water.

**only for Voltaren 50 mg enteric coated tablets*

Prolonged-release tablet

Core: cetyl alcohol, magnesium stearate, polyvinylpyrrolidone, silicone dioxide, sucrose.

Coating: hydroxypropyl methylcellulose, iron oxide red, polysorbate 80, talc, titanium dioxide, purified water.

Polish: sucrose, polyethylene glycol 8000, purified water.

3 Indications

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthrosis, and spondylarthritis.
- Painful syndromes of the vertebral column.
- Non-articular rheumatism.
- Acute attacks of gout.

4 Dosage and administration

Dosage

As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest possible duration necessary to control symptoms (see section 6 Warnings and precautions).

General target population: adults

An initial maximum daily dose of 150 mg can be used on the first day. The total maximum daily dose is 100 mg to be divided in separate doses and used for the shortest possible duration. The total daily dose should generally be divided into 2 to 3 separate doses.

Where the symptoms are most pronounced during the night or in the morning, Voltaren SR 75 and Voltaren Retard 100 should preferably be taken in the evening.

In some conditions the dose may be adjusted based on physician’s assessment, after careful consideration following risk-benefit analysis.

Special populations

Pediatric patients (below 18 years of age)

Because of their dosage strength, Voltaren 50 mg gastro-resistant tablets are not recommended for use in children and adolescents below 14 years of age; Voltaren 25 mg gastro-resistant tablets could be used in these patients; Voltaren SR 75 and Voltaren Retard 100 are not suitable for children and adolescents.

Geriatric patients (65 years or above)

Caution is indicated on basic medical grounds, especially for frail elderly patients or those with a low body weight (see section 6 Warnings and precautions).

Congestive heart failure (NYHA-I) or significant cardiovascular risk factors

Patients with congestive heart failure (NYHA-I) or patients with significant risk factors for cardiovascular disease should be treated with Voltaren only after careful consideration.

Renal impairment

Voltaren is contraindicated in patients with renal failure (GFR <15 mL/min/1.73m^2) (see section 5 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 6 Warnings and precautions).

Hepatic impairment

Voltaren is contraindicated in patients with hepatic failure (see section 5 Contraindications). No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Voltaren to patients with mild to moderate hepatic impairment (see section 6 Warnings and precautions).

Method of administration

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

5 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation (see sections 6 Warnings and precautions and 7 Adverse drug reactions).
- Last trimester of pregnancy (see section 9 Women of child-bearing potential, pregnancy, breast-feeding and fertility).
- Hepatic failure.

- Renal failure (GFR < 15 mL/min/1.73 m^2).
- Established congestive heart failure (New York Heart Association [NYHA] classification II-IV).
- Ischemic heart disease.
- Peripheral arterial disease and/or cerebrovascular disease.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Voltaren is also contraindicated in patients in whom the use of acetylsalicylic acid or other NSAIDs can precipitate asthma, angioedema, urticaria, or acute rhinitis (i.e. NSAID-induced cross-reactivity reactions) (see sections 6 Warnings and precautions and 7 Adverse drug reactions).

6 Warnings and precautions

Cardiovascular effects

- **Cardiovascular thrombotic events**

Clinical trials of several COX-2 selective and non-selective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistence evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see **Gastrointestinal effects**).

- **Hypertension**

NSAIDs, including Voltaren, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including Voltaren, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

- **Edema**

Fluid retention and edema have been observed in some patients taking NSAIDs. Voltaren should be used with cautions in patients with fluid retention.

Congestive heart failure (NYHA-I) or significant cardiovascular risk factor

Patients with congestive heart failure (NYHA-I) or patients with significant risk factors for cardiovascular disease should be treated with Voltaren only after careful consideration.

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 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.

Gastrointestinal effects

Serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine, 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. Only one in five patients, who develop a serious upper GI adverse events on NSAID therapy, is symptomatic. 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. This trends continue with longer duration of use, increasing the likelihood of developing a serious GI events at some time during the course of therapy. However, even short-term therapy is not without risk.

If gastrointestinal bleeding or ulceration occurs in patients receiving Voltaren, the treatment should be discontinued.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Voltaren in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 7 Adverse drug reactions). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation and in the elderly. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious adverse event is suspected. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

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

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

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (see section 8 Interactions).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may by exacerbated (see section 7 Adverse drug reactions).

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

Hematological 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 hemostasis should be carefully monitored.

Respiratory effects (pre-existing asthma)

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

Hepatobiliary effects

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

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

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

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including Voltaren (see section 7 Adverse drug reactions). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Voltaren should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

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

Renal effects

As fluid retention and edema have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion of any cause, e.g. before or after major surgery (see section 5 Contraindications). Monitoring of renal function is recommended as a precautionary measure when using Voltaren in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Long term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Advance renal disease

No information is available from controlled clinical studies regarding the use of Voltaren in patients with advanced renal disease. Therefore, treatment with Voltaren is not recommended in these patients with advanced renal disease. If Voltaren therapy must be initiated, close monitoring of the patient’s renal function is advisable.

Anaphylactoid reactions

As with other NSAIDs, anaphylactoid reactions may occur with diclofenac in patients without known prior exposure to the drug. Voltaren should not be given to patients with the aspirin trial. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin

or other NSAIDs (see section 5 Contraindications). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Geriatric patients

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

Interactions with NSAIDs

The concomitant use of Voltaren with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects (see section 8 Interactions).

Masking signs of infections

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

Effects on ability to drive or use machines

Patients experiencing dizziness or other central nervous disturbances should refrain from driving a vehicle or operating machines.

7 Adverse drug reactions

Tabulated summary of adverse drug reactions

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 7-1) 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 using the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), including isolated reports.

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

Table 7-1 Adverse drug reactions

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

Very rare:	Bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus.
Renal and urinary disorders	
Very rare:	Acute kidney injury (acute renal failure), hematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare:	Edema

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

Description of selected adverse drug reactions

Arteriothrombotic events

Meta-analysis and pharmacoepidemiological data point towards a small increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment (see section 6 Warnings and precautions).

Visual effects

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

8 Interactions

The following interactions include those observed with Voltaren solution for injection, gastro-resistant tablets, prolonged-released tablets, suppositories, and/or other pharmaceutical forms of diclofenac.

Observed interactions to be considered

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

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

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

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE)

inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity (see section 6 Warnings and precautions).

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

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 6 Warnings and precautions).

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

Anticipated interactions to be considered

Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 6 Warnings and precautions).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 6 Warnings and precautions). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of hemorrhage 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 6 Warnings and precautions).

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with metformin, especially in patients with pre-existing renal impairment.

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

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

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

***Aspirin*:** When Voltaren is administered with aspirin, its protein binding is reduced. The clinical significance of this interaction is not known, however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effect.

9 Women of child-bearing potential, pregnancy, breast-feeding and fertility

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. Voltaren should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. Risk of fetal renal impairment with subsequent oligohydramnios has been observed when NSAIDs (including diclofenac) were used from the 20th week of pregnancy onwards.

As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus (see sections 5 Contraindications and 13 Non-clinical safety data).

Breast-feeding

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

Fertility

As with other NSAIDs, the use of Voltaren may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Voltaren should be considered.

10 Overdosage

Symptoms

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

Therapeutic measures

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

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

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

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances (ATC code: M01AB05).

Mechanism of action (MOA)

Voltaren contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties.

Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, 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.

Pharmacodynamics (PD)

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.

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.

In clinical trials Voltaren has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin.

Voltaren SR 75 and Retard 100 are particularly suitable for patients in whom a daily dose of 75 mg or 100 mg is appropriate to the clinical picture. The possibility of prescribing the medicinal product in a single daily dose considerably simplifies long-tem treatment and helps to avoid the possibility of dosage errors. Voltaren SR 75 also allow the maximum daily dose of 150 mg to be given in a balanced b.i.d. schedule.

Pharmacokinetics (PK)

Absorption

Enteric-coated tablet

Diclofenac is completely absorbed from the gastro-resistant tablets after their passage through the stomach. Although absorption is rapid, its onset may be delayed due to the gastro-resistant coating of the tablet.

Mean peak plasma concentrations of 1.5 micrograms/mL (5 micromol/L) are attained on average 2 hours after ingestion of one tablet of 50 mg. The amount absorbed is linearly related to the size of the dose.

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

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

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

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

Prolonged-release tablet

Judged by urinary recovery of unchanged diclofenac and its hydroxylated metabolites, the same amount of diclofenac is released and absorbed from Voltaren prolonged-release tablets as from enteric-coated tablets. However, the systemic availability of diclofenac from Voltaren prolonged-release tablets is on average about 82% of that achieved with the same dose of Voltaren administered in the form of enteric coated tablets (possibly due to release-rate dependent "first-pass" metabolism). As a result of a slower release of the active substance from Voltaren prolonged-release tablets, peak concentrations attained are lower than those observed following the administration of enteric-coated tablets.

Mean peak concentrations of 0.5 micrograms/mL or 0.4 micrograms/mL (1.6 or 1.25 micromol/L) are reached on average 4 hours after ingestion of a prolonged-release tablet of 100 mg or 75 mg.

Food has no clinically relevant influence on the absorption and systemic availability of Voltaren prolonged-release tablets.

On the other hand, mean plasma concentrations of 13 ng/mL and 40 nmol/L can be recorded at 24 hours and 16 hours after administration of Voltaren prolonged release tablets 100 mg and 75 mg, respectively. The amount absorbed is linearly related to the dose strength.

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

Trough concentrations are around 22 ng/mL and 25 ng/mL (70 nmol/L and 80 nmol/L) during treatment with Voltaren prolonged-release tablets 100 mg once daily and 75 mg twice daily, respectively.

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.

Biotransformation/metabolism

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

Elimination

Total systemic clearance of diclofenac from plasma is 263 ± 56 mL/min (mean value ± SD). The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive.

About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the feces.

Linearity/non-linearity

Enteric-coated tablet

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

Prolonged-release tablet

The amount absorbed is linearly related to the dose strength.

Special populations

Geriatric patients

No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed.

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.

12 Clinical studies

Voltaren is a well-established product.

13 Non-clinical 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 5 Contraindications and 9 Women of child-bearing potential, pregnancy, breast-feeding and fertility).

14 Pharmaceutical information

Incompatibilities

Not applicable.

Storage

Do not store above 30°C. Protect from light and moisture.

Shelf life: the expiry date is indicated on the packaging.

Keep out of the reach and sight of children.

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Pack size

Voltaren 25 mg enteric-coated tablet Reg. No. DKL9930409415A1
Box, 5 blisters @ 10 enteric-coated tablets

Voltaren 50 mg enteric-coated tablet Reg. No. DKL9930409415B1
Box, 5 blisters @ 10 enteric-coated tablets

Voltaren SR 75 prolonged-release tablet Reg. No. DKL9930409514B1
Box, 5 blisters @ 10 prolonged-release tablets

Voltaren Retard 100 mg prolonged-release tablet Reg. No. DKL9930409514A1
Box, 5 blisters @ 10 prolonged-release tablets

Marketing Authorization Holder

PT Novartis Indonesia

Manufacturer

Manufactured by PT Novartis Indonesia, Jakarta, Indonesia.

Product Information based on CDS version 2.4 (04-Aug-2021)