VOLTAREN®

(diclofenac sodium)

75mg and 100mg Modified-release tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

VOLTAREN SR 75mg tablet

VOLTAREN Retard 100 modified release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

The active substance is diclofenac sodium.

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

For a full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Modified-release tablets with prolonged release of the active substance.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of:

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
- Symptomatic, short-term treatment of post-traumatic and post-operative pain (POP), inflammation, and swelling, e.g. following dental or orthopaedic surgery.
- Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis.

4.2. Posology and method of administration

Posology

As a general recommendation, the dose should be individually adjusted.

The tablets should be swallowed whole with liquid, preferably with meals and must not be divided or chewed.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

General target population: adults

The recommended initial daily dose is 100 to 150 mg, administered as 1 tablet of Voltaren Retard 100 mg or as 2 tablets of Voltaren SR 75 mg.

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

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

The tablets should be taken whole with liquid, preferably with meals.

Pediatric patients (below 18 years of age)
With regard to tablets 75/100 mg a use in children and adolescents is not recommended

Geriatric patients (aged 65 years 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 Special warnings and precautions for use).

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

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

Renal impairment

Voltaren is contraindicated in patients with renal failure (GFR<15mL/min./1.73m^2) (see section 4.3 Contraindications).

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

Hepatic impairment

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

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

Method of administration

The tablets should be taken whole with liquid preferably with meals.

4.3. Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Last trimester of pregnancy (see section 4.6 Fertility, pregnancy and lactation).
- Hepatic failure
- Renal failure (GFR<15mL/min./1.73m^2)
- 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 section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

- Established congestive heart failure (NYHA II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4. Special warnings and precautions for use

General

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

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

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

Voltaren PR tablets contain sucrose and sodium

Voltaren prolonged-release tablets contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

Gastrointestinal effects

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Diclofenac, the treatment should be discontinued.

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.
As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Voltaren in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.7 Undesirable effects). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with 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)/aspirin or other drugs likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section 4.7 Undesirable effects).

Hepatobiliary effects

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

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Voltaren, 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 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.

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and generalised bullous fixed drug eruption have been reported very rarely in association with the use of diclofenac (see 4.8 Undesirable effects). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Voltaren should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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

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

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

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

Hematologic effects
During prolonged treatment with Voltaren, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, Voltaren may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

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

Geriatric patients

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

Interactions with NSAIDs

The concomitant use of Voltaren with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to undesirable effects (see section 4.5 Interactions with other medicinal products and other forms of interactions).

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

4.5. Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with Voltaren modified-released tablets 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 sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac.

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

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

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. (see section 4.4 Special warnings and precautions for use).

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 and tacrolimus.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4 Special warnings and precautions for use).

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

Anticipated interactions to be considered

Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4 Special warnings and precautions for use).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4 Special warnings and precautions for use). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and precautions for use).

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy. There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with metformin, especially in patients with pre-existing renal impairment.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.
Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.
Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

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

4.6. Fertility, pregnancy and lactation

Women of child-bearing potential

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

Pregnancy

There are insufficient data on the use of diclofenac in pregnant women. . Some epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy, however the overall data are inconclusive.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %.
The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.
In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. During the first and second trimester of pregnancy, Voltaren should not be given unless clearly necessary. If Voltaren is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for

oligohydramnios should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios is found.

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

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

the mother and the neonate, at the end of pregnancy, to:

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

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

Lactation

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

Fertility

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

4.7. Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 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 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); Not known: cannot be estimated from the available data. The following undesirable effects include those reported with Voltaren modified-release tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Table 1

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.
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.
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 hemorrhage, hematemesis, hemorrhagic diarrhoea, melena, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis or perforation which may lead to peritonitis).
Very rare:	Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, intestinal diaphragm disease, pancreatitis.
Not known	Ischemic colitis
Hepatobiliary disorders	
Common:	Transaminases increased.
Rare:	Hepatitis, jaundice, liver disorder.
Very rare:	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	

Common:	Rash.
Rare:	Urticaria.
Very rare:	Bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus.
Not Known:	Fixed drug eruption, Generalised bullous fixed drug eruption
Renal and urinary disorders	
Very rare:	Acute kidney injury (acute renal failure) hematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare:	Edema.

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

Description of selected adverse drug reactions

Arteriothrombotic events

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

Visual effects

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

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal hemorrhage, 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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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, 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 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.

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.

Voltaren SR 75 mg and Voltaren Retard 100 mg modified-release tablets 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 mg modified-release tablets also allow the maximum daily dose of 150 mg to be given in a balanced b.i.d. schedule.

5.2 Pharmacokinetic properties

Absorption

Judged by urinary recovery of unchanged diclofenac and its hydroxylated metabolites, the same amount of diclofenac is released and absorbed from Voltaren modified-release tablets as from gastro-resistant tablets. However, the systemic availability of diclofenac from Voltaren modified-release tablets is on average about 82% of that achieved with the 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 modified-release tablets, peak concentrations attained are lower than those observed following the administration of gastro-resistant 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 modified-release tablet of 100 mg or 75 mg.

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

On the other hand, mean plasma concentrations of 13 ng/mL (40 nmol/L) can be recorded at 24 hours (16 hours) after administration of Voltaren Retard 100 mg (Voltaren SR 75 mg). 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.

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

Trough concentrations are around 22 ng/mL or 25 ng/mL (70 nmol/L or 80 nmol/L) during treatment with Voltaren Retard 100 mg once daily or Voltaren SR 75 mg twice daily.

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

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

Voltaren is a well established product.

5.3. Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. In standard preclincal animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac had no influence on the fertility of parent animals in rats. Except for minimal fetal effects at maternally toxic doses, the prenatal, perinatal and postnatal development of the offspring was not affected.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The

slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors (see sections 4.3 Contraindications and 4.6 Fertility, pregnancy and lactation).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Voltaren SR 75 mg: Cetyl alcohol; magnesium stearate; povidone; silica aerogel; colloidal anhydrous; sucrose; hypromellose; iron oxide red (E172); macrogol 8000; polysorbate 80; sucrose; talc; titanium dioxide (E171), purified water, ethanol with 5% isopropyl.

Voltaren Retard 100 mg: Cetyl alcohol; magnesium stearate; povidone; silica aerogel; colloidal anhydrous; sucrose; hypromellose; iron oxide red (E172); macrogol 8000; polysorbate 80; sucrose; talc; titanium dioxide (E171), purified water, ethanol with 5% isopropyl.

6.2. Incompatibilities

None known.

6.2. Shelf life

Voltaren SR 75 mg: 3 years
Voltaren Retard 100 mg: 3 years

6.3. Special precautions for storage

Voltaren SR 75 mg: protect from heat (store below 30°C) and moisture.
Voltaren Retard 100 mg: none
Medicines should be kept out of the reach of children.

6.4. Nature and contents of container

Voltaren SR 75 mg: Thermoformed blisters using rigid plastic films backed with a heat-sealable lacquered aluminum foil; HDPE bottles.
Voltaren Retard 100mg: Thermoformed blisters using rigid plastic films backed with a heat-sealable lacquered aluminum foil.
Pack size/s:
Voltaren SR 75 mg: 10, 20, 28, 56, 70, 100 tablets
Voltaren Retard 100 mg: 10, 28, 70 tablets
Not all pack sizes may be marketed.

6.5. Instructions for use/handling

Voltaren SR and Voltaren Retard tablets should be swallowed whole, preferably with meals.

7. MARKET AUTHORISATION HOLDER

Novartis Ireland Limited
Vista Building,
Elm Park, Merrion Road,
Ballsbridge, Dublin 4,
Ireland.

8. MARKET AUTHORISATION NUMBER

Voltaren SR 75 mg: MA1249/00708
Voltaren Retard 100mg: MA1249/00709

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 25th October 2005
Date of latest renewal: 30th September 2013

10. DATE OF REVISION OF THE TEXT

24th September 2025