NOVARTIS

Drug Regulatory Affairs

VOLTAREN®

(diclofenac sodium)

75 mg and 100 mg Prolonged-release tablets

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Trade name of the medicinal product

VOLTAREN® 75 mg prolonged-release tablets.

VOLTAREN® 100 mg prolonged-release tablets.

2 Qualitative and quantitative composition

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

One prolonged-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

Film-coated tablets.

Information might differ in some countries.

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 [1,8,39-41].
- Post-traumatic and post-operative pain, inflammation, and swelling, e.g. following dental or orthopaedic surgery [18-22,55,58,59].
- Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis [23-26,60].

4.2. Posology and method of administration

As a general recommendation, the dose should be individually adjusted and the lowest effective dose given for the shortest possible duration [223].

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

Adults

The recommended initial daily dose is 100 to 150 mg, administered as 1 tablet of Voltaren® prolonged-released 100 mg or as 2 tablets of Voltaren prolonged-released 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 prolonged-release 75 mg and 100 mg should preferably be taken in the evening.

Children and adolescents

Because of their dosage strength, Voltaren prolonged-release tablets 75 mg and 100 mg are not suitable for children and adolescents [223].

4.3. Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation [224].
- Last trimester of pregnancy (see section 4.6 Pregnancy and lactation) [224].
- Severe hepatic renal and cardiac failure (see section 4.4 Special warnings and precautions for use) [224].
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Voltaren is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs [98,99].

4.4. Special warnings and precautions for use

Warnings

Gastrointestinal bleeding, ulceration or perforation, 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 [179]. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Voltaren, the medicinal product should be withdrawn [224].

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 4.8 Undesirable effects). 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 [224].

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

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

Precautions

General

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 [224].

Caution is indicated in the elderly on basic medical grounds [101]. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Voltaren prolonged-release tablets contain sucrose and therefore are not recommended for patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria [224].

Gastrointestinal effects

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Voltaren in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8 Undesirable effects). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly [224].

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 [224].

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products likely to increase gastrointestinal risk [224].

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) [224].

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section 4.8 Undesirable effects) [224].

Hepatic effects

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

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

Caution is called for when using Voltaren in patients with hepatic porphyria, since it may trigger an attack [102-104].

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 [100], history of hypertension [224], 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) [63,224]. 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.

Haematological effects

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

Like other NSAIDs, Voltaren may temporarily inhibit platelet aggregation [57,105]. Patients with defects of haemostasis should be carefully monitored [106,107].

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

The following interactions include those observed with Voltaren prolonged- released tablets and/or other pharmaceutical forms of diclofenac.

Lithium: If used concomitantly, diclofenac may raise plasma concentrations of lithium [64]. Monitoring of the serum lithium level is recommended [224].

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin [65,66]. Monitoring of the serum digoxin level is recommended [229].

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. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4 Special warnings and precautions for use) [67,68,224].

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) [70,224].

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) [224]. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly [46-48,92]. Close monitoring of such patients is therefore recommended [46-48,71].

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) [224].

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect [50-52]. 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.

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 [72].

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins [93,95-97]. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin [224].

Quinolone antibacterials: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs [194].

Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a

significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism [232].

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin [232].

4.6. Pregnancy and lactation

Pregnancy

The use of diclofenac in pregnant women has not been studied. Therefore, Voltaren should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweights the risk to the foetus [108,162]. 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 section 4.3 Contraindications) [108,162]. Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3 Preclinical safety data) [224].

Lactation

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, Voltaren should not be administered during breast feeding in order to avoid undesirable effects in the infant [30,224].

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 [224].

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 [224].

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

Table 1 [224]

Blood and lymphatic system disorders

Very rare:	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis [145-151].
Immune system disorders	
Rare:	Hypersensitivity, anaphylactic and anaphylactoid reactions [152] (including hypotension and shock) [224].
Very rare:	Angioneurotic oedema (including face oedema) [224].
Psychiatric disorders	
Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder [84,87,121,122].
Nervous system disorders	
Common:	Headache, dizziness [11,84,87].
Rare:	Somnolence [84].
Very rare:	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis [84,87,121,122], taste disturbances [84,87,121,122,160,161], cerebrovascular accident [224].
Eye disorders	
Very rare:	Visual disturbance, vision blurred, diplopia [84,87,160,161].
Ear and labyrinth disorders	
Common:	Vertigo [11,84,87].
Very rare:	Tinnitus, hearing impaired [84,87,160,161].
Cardiac disorders	
Very rare:	Palpitations, chest pain, cardiac failure [101,157-159], myocardial infarction [224].
Vascular disorders	
Very rare:	Hypertension [101,157-159], vasculitis [125,153-156].
Respiratory, thoracic and mediastinal disorders	
Rare:	Asthma (including dyspnoea) [152].
Very rare:	Pneumonitis [125,153-156].
Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia [11,109].
Rare:	Gastritis [224], gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation) [11,84,87,109,110,113,116,117].
Very rare:	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis [109-116,118-120].
Hepatobiliary disorders	
Common:	Transaminases increased [11].
Rare:	Hepatitis, jaundice [140-143], liver disorder [224].
Very rare:	Fulminant hepatitis [144], hepatic necrosis, hepatic failure [230].
Skin and subcutaneous tissue disorders	
Common:	Rash [11,84,87].
Rare:	Urticaria [123].
Very rare:	Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell’s syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura [124-130], allergic purpura, pruritus [224].
Renal and urinary disorders	

Very rare:	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis [131-139].
General disorders and administration site conditions	
Rare:	Oedema [84,87].

4.9. Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible [163-165,224].

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 [163-165].

Special measures such as forced diuresis, dialysis, or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism [164].

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 [224].

5 Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of action

Voltaren contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties [1,9]. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action [2]. 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 [89,90].

Pharmacodynamic effects

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac 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 [1].

In post-traumatic and post-operative inflammatory conditions, Voltaren rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

Voltaren 75 mg and 100 mg prolonged-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 75 mg prolonged-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 prolonged-release tablets as from gastro-resistant tablets [76]. 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 gastro-resistant tablets (possibly due to release-rate dependent "first-pass" metabolism) [189,190]. 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 gastro-resistant tablets [189].

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 [189,190].

Food has no clinically relevant influence on the absorption and systemic availability of Voltaren prolonged-release tablets [189].

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 prolonged-release tablets 100 mg (75 mg) [189,190]. The amount absorbed is linearly related to the dose strength [189].

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 [78,80,166].

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed [7].

Trough concentrations are around 22 ng/mL or 25 ng/mL (70 nmol/L or 80 nmol/L) during treatment with Voltaren prolonged-release tablets 100 mg once daily or 75 mg twice daily [189,191].

Distribution

99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%) [6]. The apparent volume of distribution calculated is 0.12 to 0.17 L/kg [80,167].

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to4 hours after peak plasma values have been attained [7,81]. 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 [7,81,168].

Biotransformation

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-,4'-hydroxy-,5-hydroxy-,4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates [82,83,169]. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac [170].

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 [80]. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours [171]. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive [169].

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 [83]. The rest of the dose is eliminated as metabolites through the bile in the faeces [31,172,193].

Characteristics in patients

No relevant age-dependent differences in the drug’s absorption, metabolism, or excretion have been observed [7,172,173,225].

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 [31,85,86]. 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 [31].

In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease [69].

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 [226-228]. There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits [174,175].

Diclofenac had no influence on the fertility of parent animals in rats. The prenatal, perinatal and postnatal development of the offspring was not affected [226].

6. Pharmaceutical particulars

6.1. List of excipients

Tablet core: Sucrose; cetyl alcohol; povidone; magnesium stearate; silica colloidal anhydrous.

Tablet coating: Hypromellose; purified talc; polysorbate 80; titanium dioxide (E171); red iron oxide (E 172).

Polishing solution: Sucrose; polyethylene glycol 8000.

Printing ink: Black (Opacode S-1-8015).

Shellac; medicinal charcoal.

Information might differ in some countries.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

Information might differ in some countries.

6.4. Special precautions for storage

Do not store above 30°C.

Store in the original package.

Voltaren prolonged-release tablets must be kept out of the reach and sight of children.

Information might differ in some countries.

6.5. Nature and contents of container

Country specific.

6.6. Instructions for use/handling

No special requirements.

This is a non-referenced document.