NOVARTIS

Regulatory Affairs

VOLTFAST® (diclofenac potassium) 50 mg Powder for oral solution

Core Data Sheet

Version 2.2

NOTICE

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

The Novartis CDS contains all relevant information relating to indications, dosing, pharmacovigilance and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

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1 Trade name

VOLTFAST® 50 mg powder for oral solution.

2 Description and composition

Pharmaceutical form

Powder for oral solution.

Homogenous, white to light yellow powder.

Active substance

The active ingredient is diclofenac potassium.

One Voltfast® sachet contains 50 mg of diclofenac potassium.

Active moiety

Diclofenac

Excipients

Potassium hydrogen carbonate; mannitol; aspartame; saccharin sodium; glyceryl dibehenate; mint flavor; anise flavor.

Information might differ in some countries.

3 Indications

Short-term treatment in the following acute conditions:

- Post-traumatic pain, inflammation and swelling, e.g. due to sprains [148].
- Post-operative pain, inflammation and swelling, e.g. following dental or orthopedic surgery [20,149-156,170,171].
- Painful and/or inflammatory conditions in gynecology, e.g. primary dysmenorrhea or adnexitis [157,158].
- Migraine attacks [166,167,169,171].
- Painful syndromes of the vertebral column.
- Non-articular rheumatism.
- As an adjuvant in severe painful inflammatory infections of the ear, nose, or throat, e.g. pharyngotonsillitis, otitis [159,161-163]. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

4 Dosage and administration

Dosage

As a general recommendation, the dose should be individually adjusted [172]. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 6 Warnings and precautions) [185].

General target population: adults

The recommended initial daily dose is 100 to 150 mg. In milder cases, 50 to 100 mg daily are usually sufficient. The daily dose should generally be divided in up to 3 separate doses.

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

In migraine, an initial dose of 50 mg should be taken at the first signs of an impending attack. In cases where pain relief within 2 hours after the first dose is not sufficient, a further dose of 50 mg may be taken. If needed, further doses of 50 mg may be taken at intervals of 4 to 6 hours, not exceeding a total dose of 200 mg per day.

Special populations

Pediatric patients (below 18 years of age)

Voltfast 50 mg powder for oral solution is not recommended for use in children and adolescents below 14 years of age. For treatment in children and adolescents below 14 years of age, oral drops and suppositories of diclofenac 12.5 mg and 25 mg are available.

For adolescents aged 14 years and over, 50 to 100 mg daily are usually sufficient, given as 1 to 2 divided doses.

The maximum daily dose of 150 mg should not be exceeded [172].

The use of Voltfast 50 mg powder for oral solution in migraine attacks has not been established in children and adolescents.

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 6 Warnings and precautions) [182,186].

Established cardiovascular disease or significant cardiovascular risk factors

Treatment with Voltfast is generally not recommended in patients with established cardiovascular disease or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease should be treated with Voltfast only after careful consideration and only at doses ≤100 mg daily if treated for more than 4 weeks (see section 6 Warnings and precautions) [185].

Renal impairment

Voltfast 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 Voltfast to patients with renal impairment (see section 6 Warnings and precautions) [185,186].

Hepatic impairment

Voltfast 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 Voltfast to patients with mild to moderate hepatic impairment (see section 6 Warnings and precautions) [185].

Method of administration

The contents of the sachet should be dissolved with stirring in a glass of natural (noncarbonated) water. The solution may remain slightly opalescent, but this should not influence the efficacy of the preparation. The solution should be swallowed preferably before meals.

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) [173].
- Last trimester of pregnancy (see section 9 WOCBP, pregnancy, breast-feeding and fertility) [173].
- Hepatic failure.
- Renal failure (GFR <15 mL/min/1.73m^2) [186].
- Severe cardiac failure (see section 6 Warnings and precautions) [173].
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Voltfast 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 crossreactivity reactions) [187] (see sections 6 Warnings and precautions and 7 Adverse drug reactions) [78,79].

6 Warnings and precautions

Gastrointestinal effects

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 [145]. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Voltfast, the treatment should be discontinued [173].

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercized when prescribing Voltfast 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 [173].

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 [173].

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 [173].

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) [173].

Close medical surveillance and caution should also be exercized in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section 7 Adverse drug reactions) [173].

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using Voltfast after gastro-intestinal surgery [188].

Cardiovascular effects

Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, may be associated with a small increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke) [183].

Treatment with Voltfast is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking) should be treated with Voltfast only after careful consideration and only at doses ≤100 mg daily when treatment continues for more than 4 weeks.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. 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 [185].

Hematologic effects

Use of Voltfast is recommended only for short-term treatment. If, however, Voltfast is used for a prolonged period, monitoring of the blood count is recommended, as with other NSAIDs.

Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation [22,85]. Patients with defects of hemostasis should be carefully monitored [86,87].

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 [173].

Hepatobiliary effects

Close medical surveillance is required when prescribing Voltfast 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 Voltfast, 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), Voltfast should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using Voltfast in patients with hepatic porphyria, since it may trigger an attack [82-84].

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 Voltfast (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. Voltfast should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity [173]. 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 [80], history of hypertension [173], 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 and after major surgery (see section 5 Contraindications) [44,173]. Monitoring of renal function is recommended as a precautionary measure when using Voltfast in such cases. Discontinuation of therapy is normally followed by a recovery to the pre-treatment state.

Geriatric patients

Caution is indicated in the elderly on basic medical grounds, especially in frail elderly patients or those with a low body weight [81,186].

Interactions with other NSAIDs

The concomitant use of Voltfast with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the potential for additive undesirable effects (see section 8 Interactions) [173].

Special excipients

Voltfast contains a source of phenylalanine and may be therefore harmful for patients with phenylketonuria.

Masking signs of infections

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

7 Adverse drug reactions

Tabulated summary of adverse drug reactions

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

The following undesirable effects include those reported with Voltfast powder for oral solution and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Table 7-1 Adverse drug reactions [173,183]

Blood and lymphatic system dis	
Very rare:	Thrombocytopenia, leukopenia, anemia (including hemolytic and aplastic anaemia), agranulocytosis [24,125-130].
Immune system disorders	
Rare:	Hypersensitivity, anaphylactic and anaphylactoid reactions [131] (including hypotension and shock) [173].
Very rare:	Angioedema (including faceedema) [173].
Psychiatric disorders	
Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder [32,34,101,102].

Nervous system disorders	
Common:	Headache, dizziness [24,32,34].
Rare:	Somnolence [34].
Very rare:	Paresthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis [32,34,101,102], dysgeusia [32,34,139,140], cerebrovascular accident [173].
Eye disorders	
Very rare:	Visual impairment, blurred vision, diplopia [32,34,139,140].
Ear and labyrinth disorders	
Common:	Vertigo [24,32,34].
Very rare:	Tinnitus, impaired hearing [32,34,139,140].
Cardiac disorders	
Uncommon* [185]:	Myocardial infarction [173], cardiac failure [81,136-138], palpitations, chest pain.
Frequency not known	Kounis syndrome [187]
Vascular disorders	
Very rare:	Hypertension [81,136-138], vasculitis [105,132-135].
Respiratory, thoracic and mediastinal disorders	
Rare:	Asthma (including dyspnea) [131]. Very rare: Pneumonitis [105,132-135].

Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, decreased appetite [24,89].
Rare:	Gastritis [173], gastrointestinal hemorrhage, hematemesis, melena, hemorrhagic diarrhea, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis, or perforation, which may lead to peritonitis) [24,32,34,89,90,93,96,97,186].
Very rare:	Colitis (including hemorrhagic colitis, ischemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, intestinal diaphragm disease, pancreatitis [89-96,98-100,186].
Hepatobiliary disorders	
Common:	Transaminases increased [24].
Rare:	Hepatitis, jaundice [120-123], liver disorder [173].
Very rare:	Fulminant hepatitis [124], hepatic necrosis, hepatic failure [179].
Skin and subcutaneous tissue	**isorders**
Common:	Rash [24,32,34].
Rare	Urticaria [79,103].
Very rare:	Bullous dermatitis, eczema, erythema, erythema multiforme, StevensJohnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schoenlein purpura [104-110], pruritus [173].
Renal and urinary disorders	
	Very rare: Acute kidney injury (acute renal failure), hematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis [111-119,186].
General disorders and administration site conditions	
Rare:	Edema [32,34].

* The frequency reflects data from long-term treatment with a high dose (150 mg daily) [185].

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) [185].

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 [186].

8 Interactions

The following interactions include those observed with Voltfast powder for oral solution 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 [180,186].

Lithium: If used concomitantly, diclofenac may raise plasma concentrations of lithium [27]. Monitoring of the serum lithium level is recommended [169].

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin [28,29]. Monitoring of the serum digoxin level is recommended [178].

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) [30,31,173].

Ciclosporin and tacrolimus: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin and tacrolimus due to the effect on renal prostaglandins [55-58]. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin or tacrolimus [173,186].

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) [173,181].

Quinolone antibacterials**:** There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs [146].

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) [33,173].

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 6 Warnings and precautions) [173]. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants [36-38], there are reports of an increased risk of hemorrhage in patients receiving diclofenac and anticoagulants concomitantly [59,186]. Close monitoring of such patients is therefore recommended [36-38,42].

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) [173].

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect [39-41]. 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 coadministered with metformin, especially in patients with pre-existing renal impairment [186].

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin [180].

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 [17].

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 [186].

9 Women of child-bearing potential, pregnancy, breastfeeding 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 [187]. Voltfast should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the foetus. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia, fetal renal impairment with subsequent oligohydramnios and/or premature closure of the ductus arteriosus (see sections 5 Contraindications and 13 Non-clinical safety data) [16,186].

Breast-feeding

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, Voltfast should not be administered during breast feeding in order to avoid undesirable effects in the infant [16,26,61,173].

Fertility

As with other NSAIDs, the use of Voltfast 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 Voltfast should be considered [173].

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 [173].

Therapeutic measures

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment [142-144]. 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 [143].

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 lifethreatening overdose [173].

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

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

Mechanism of action (MOA)

Voltfast contains the potassium salt of diclofenac, a non-steroidal compound with pronounced antirheumatic, analgesic, anti-inflammatory, and antipyretic properties [1,3,43].

Voltfast has a rapid onset of action, which makes it particularly suitable for the treatment of acute painful and inflammatory conditions [20]. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered to be fundamental to its mechanism of action [21]. Prostaglandins play a major role in causing inflammation, pain, and fever.

Diclofenac potassium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans [53,54].

Pharmacodynamics (PD)

Voltfast has been found to exert a pronounced analgesic effect in moderate and severe pain. In the presence of inflammation, e.g. due to trauma or following surgical interventions, it rapidly relieves both spontaneous pain and pain on movement and diminishes inflammatory swelling and wound edema [20,147-156]. Clinical studies have also revealed that in primary dysmenorrhoea the active substance is capable of relieving the pain and reducing the extent of bleeding [23,25,157,158]. In migraine attacks Voltfast has been shown to be effective in relieving the headache and in improving the accompanying symptoms nausea and vomiting [166,167].

Pharmacokinetics (PK)

Absorption

Diclofenac is rapidly and completely absorbed from diclofenac potassium [9,63,168]. Mean peak plasma concentrations of 5.5 micromol/L are attained after 5 to 20 minutes after ingestion of one sachet of 50 mg [168].

Ingestion together with food is expected to have no influence on the amount of diclofenac absorbed although onset and rate of absorption may be slightly delayed [10,12,63].

Since about half of diclofenac is metabolized during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) is about half as large following oral or rectal administration as it is following a parenteral dose of equal size [4,15,65].

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed [16,63].

Distribution

99.7% of diclofenac binds to serum proteins, mainly to albumin (99.4%) [8,68]. The apparent volume of distribution calculated is 0.12 to 0.17 L/kg [4,68,70].

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been reached [16]. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma levels, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours [16,68,71,72].

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 [181].

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'-hydroxy4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates [6,7,68,73]. Two of these phenolic metabolites are biologically active, but to a much lesser extent than diclofenac [74].

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 [4]. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours [75]. One metabolite, 3’hydroxy-4’-methoxy-diclofenac, has a much longer plasma half-life. However, this metabolite is virtually inactive [73].

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 [7]. The rest of the dose is eliminated as metabolites through the bile in the faeces [18,68,76,77].

Linearity/non-linearity

The amount absorbed is in linear proportion to the size of the dose [11,15,63].

Special populations

Geriatric patients: No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed [16,60,68,76,174].

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 [5,13,68]. 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 [18].

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 [19,68].

12 Clinical studies

Voltfast is a well established product.

13 Non-clinical safety data [184]

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 [175-177]. In standard preclinical animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits [69].

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 [175].

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 WOCBP, pregnancy, breastfeeding and fertility).

14 Pharmaceutical information

Incompatibilities Not

applicable.

Special precautions for storage

Do not store above 25°C.

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

Voltfast powder for oral solution must be kept out of the reach and sight of children.

Information might differ in some countries.

Instructions for use and handling

No special requirements.