NOVARTIS

Voltfast®

Composition
Active substance: Diclofenac potassium (phenylacetic acid derivative)

Pharmaceutical form and quantity of active substance per unit
Sachet with powder for oral solution, containing 50 mg diclofenac potassium. Homogeneous white to faintly yellowish powder.

Indications / Potential uses
Short-term treatment (maximum: 3 days) of the following acute conditions:
- Postoperative inflammation and pain, e.g. following dental or orthopaedic surgery.
- Painful post-traumatic inflammatory states, e.g. due to sprains.
- Painful and/or inflammatory gynaecological conditions, e.g. primary dysmenorrhoea or adnexitis.
- Migraine attacks, with or without aura
- As an adjunct in severe, painful, inflammatory infections of the ear, nose or throat, e.g. pharyngotonsillitis, otitis.
- Painful syndromes of the vertebral column.
- Non-articular rheumatism.

In keeping with standard therapeutic principles, the underlying disease should be treated with specific therapy as appropriate. Fever alone is not an indication.

Dosage and Administration
As a general recommendation, the dose should be individually adjusted, and the lowest effective dose should be given for the shortest possible period of time.

Adults
The usual dosage is 2–3 sachets of Voltfast (100–150 mg) daily. In milder cases, as well as for children over 14 years of age, 2 sachets of Voltfast daily (50–100 mg) are usually sufficient. The total daily amount should normally be given in 2–3 divided doses.
In primary dysmenorrhoea the daily dosage should be individually adjusted and is generally 1–3 sachets. Initially a dose of 1–2 sachets should be prescribed.

Migraine
An initial dose of 50 mg is recommended at the first sign of an impending attack. A further 50 mg dose may be taken if pain relief is inadequate approx. 2 hours after ingestion of the first dose. If necessary, additional 50 mg doses may be taken at intervals of 6-8 hours, but the maximum dose of 150 mg within a 24 hour period must not be exceeded.

Children
Because of its strength, Voltfast is not recommended for use in children below 14 years of age.
Voltaren oral drops and Voltaren 12.5 mg and 25 mg suppositories are available for use in children.
At present no data are available on the use of Voltfast in the treatment of migraine attacks in children.

Administration
Stir to dissolve the contents of a sachet in a glass of (non-carbonated) water, then drink. The solution may remain somewhat cloudy, but this has no effect on the efficacy of the medicinal product. The solution should preferably be taken before meals.

Contraindications
- Hypersensitivity to the active substance or to any of the excipients indicated under **Composition**.
- A history of bronchospasm, urticaria, acute rhinitis, nasal polyps or allergy-like symptoms after taking acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.
- Third trimester of pregnancy (see **Pregnancy and Lactation**).
- Active gastric and/or duodenal ulcers, gastrointestinal bleeding or perforation
- Inflammatory bowel disease (such as Crohn's disease or ulcerative colitis).
- Severe hepatic dysfunction (Child-Pugh class C; cirrhosis and ascites).
- Severe renal impairment (creatinine clearance < 30 ml/minute).
- Severe heart failure (NYHA III–IV).
- Treatment of postoperative pain after coronary bypass surgery (or use of a heart-lung machine).
- Children under 14 years of age.

Warnings and Precautions
General warning for the use of systemic nonsteroidal anti-inflammatory drugs
Gastrointestinal ulceration, bleeding or perforation may occur at any time during treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), whether COX-2 selective or not, even in the absence of warning symptoms or a predisposing history. To minimize this risk, the lowest effective dose should be given for the shortest possible duration of treatment.
Patients with gastrointestinal disorders, hepatic dysfunction or a history suggestive of peptic ulcer should not use this medicinal product unless it is strictly indicated, and should be kept under close medical supervision during treatment.
Placebo-controlled studies have shown an increased risk of thrombotic cardiovascular and cerebrovascular complications with certain selective COX-2 inhibitors. It is not yet known whether this risk correlates directly with the COX-1 / COX-2 selectivity of individual NSAIDs. As no comparable clinical study data are available at present for long-term treatment with the maximum dosage of diclofenac, the possibility of a similarly elevated risk cannot be ruled out. Until such data become available, a careful risk-benefit assessment must be carried out prior to using diclofenac in patients with clinically confirmed coronary heart disease, cerebrovascular disorders, peripheral arterial occlusive disease or considerable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking). Due to this risk, too, the lowest effective dose should be given for the shortest possible duration of treatment.
The renal effects of NSAIDs include fluid retention with oedema and/or arterial hypertension. For this reason, diclofenac should be used with caution in patients with cardiac dysfunction and other conditions that predispose to fluid retention. Caution is also indicated in patients who take concomitant diuretics or ACE inhibitors, or who are at increased risk of hypovolaemia.
The consequences are generally more serious in the elderly. If gastrointestinal bleeding or ulceration occurs in patients undergoing treatment with Voltfast, the medicinal product should be withdrawn.
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 **Adverse effects**). Patients appear to be at highest risk at the start of treatment, with the onset of the reaction usually occurring within the first month of treatment. Voltfast should be discontinued at the first sign of rash, mucosal lesions or any other sign of hypersensitivity.
As with other NSAIDs, allergic reactions – including anaphylactic/anaphylactoid reactions – may occur in rare cases, even without prior exposure to diclofenac.
Its pharmacodynamic properties mean that, like other NSAIDs, Voltfast may mask the signs and symptoms of infection.

Precautions
General
Concomitant use of Voltfast with systemic NSAIDs, such as cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence of synergistic benefits, and due to the potential for additive adverse effects.
Caution is required in elderly patients on basic medical grounds. In particular, it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight.

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

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions to NSAIDs such as asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, particular caution is required in such patients (emergency readiness). This also applies to patients with allergic reactions – e.g. rash, pruritus or urticaria – to other substances.

Gastrointestinal effects

As with all NSAIDs, including diclofenac, close medical surveillance is required and particular caution should be exercised 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 **Adverse effects**). The risk of GI bleeding is greater with higher NSAID doses, as it also is in patients with a history of ulcer (particularly if complicated by bleeding or perforation) and in elderly patients.

Treatment should be initiated and maintained at the lowest effective dose in order to reduce the risk of GI toxicity in patients with a history of ulcer (particularly if complicated by bleeding or perforation) and in elderly patients.

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 that may increase gastrointestinal risk.

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

Hepatic effects

Close medical surveillance is required when giving Voltfast to patients with hepatic impairment, as their condition might be exacerbated (see **Adverse effects**).

As with all NSAIDs, including diclofenac, levels of one or more liver enzymes may rise during treatment with Voltfast. This has been observed very frequently with diclofenac in clinical studies (in approx. 15% of patients), but is very rarely accompanied by clinical symptoms. Most of these cases involve borderline increases. Frequently (in 2.5% of cases) the increases observed were moderate (≥ 3–< 8 times the upper limit of normal), while the incidence of marked increases (≥ 8 times the upper limit of normal) remained around 1%. Raised liver enzyme levels were accompanied by clinically manifest liver damage in 0.5% of cases in the above-mentioned clinical studies. Elevated enzyme levels were generally reversible after discontinuation of the drug.

It should be noted, however, that Voltfast is recommended for short-term treatment only (not more than 3 days).

Voltfast should be discontinued if abnormal liver function tests persist or worsen, if clinical signs or symptoms suggestive of liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash).

In addition to elevated liver enzymes, there have been rare reports of severe hepatic reactions – including jaundice and, very rarely, fulminant hepatitis, hepatic necrosis and hepatic failure which, in isolated cases, had a fatal outcome.

Hepatitis may develop without prodromal symptoms in patients using diclofenac. Caution is required when using Voltfast in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

Owing to the importance of prostaglandins in maintaining renal blood flow, prolonged treatment with high doses of NSAIDs, including diclofenac, frequently (1–10%) results in oedema and hypertension.

Particular caution is required in patients with impaired cardiac or renal function, in patients with a history of hypertension, in elderly patients, in patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see **Contraindications**). Monitoring of renal function is recommended as a precautionary measure when using Voltfast in such cases. Patients usually recover to their pre-treatment state following discontinuation of therapy.

Haematological effects

Voltfast is recommended for short-term use only. As with other NSAIDs, regular blood counts are recommended if Voltfast is nonetheless used for prolonged periods.

Like other NSAIDs, Voltfast may temporarily inhibit platelet aggregation. Patients with coagulation disorders should be closely monitored.

Interactions

The following interactions were observed with Voltfast and/or other dosage forms of diclofenac.

Lithium

Diclofenac may increase plasma concentrations of concomitantly administered lithium. Monitoring of serum lithium levels is recommended.

Digoxin

Diclofenac may increase plasma concentrations of concomitantly administered digoxin. Monitoring of serum digoxin levels is recommended.

Diuretics and antihypertensive agents

As with other NSAIDs, concomitant use of diclofenac may reduce the antihypertensive effects of diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme [ACE] inhibitors). The combination should therefore be administered with caution, and patients – especially elderly patients – should have their blood pressure monitored regularly. Patients should be adequately hydrated, and attention should be paid to monitoring renal function on initiating combination therapy, and regularly thereafter, particularly due to the increased risk of nephrotoxicity with diuretics and ACE inhibitors. Concomitant treatment with potassium-sparing drugs may increase serum potassium levels, which should therefore be monitored frequently (see **Warnings and Precautions**).

Other NSAIDs and corticosteroids

Concomitant administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal adverse effects (see **Warnings and Precautions**).

Anticoagulants and antiplatelet agents

Caution is required since concomitant administration could increase the risk of bleeding (see **Warnings and Precautions**).

Although nothing was seen in clinical investigations to suggest that diclofenac affects the action of anticoagulants, there have been isolated reports of an increased risk of bleeding 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 **Warnings and Precautions**).

Antidiabetic agents

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 reactions following administration of diclofenac, necessitating adjustment of the dosage of the antidiabetic. For this reason, monitoring of blood glucose levels is recommended as a precautionary measure during combination therapy.

Methotrexate

Caution is required when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate because blood levels of methotrexate may rise, and methotrexate toxicity may increase.

Ciclosporin

Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to its effects on renal prostaglandins. It should therefore be given at doses lower than those that would be used in patients not receiving ciclosporin.

Quinolone antibiotics
There have been isolated reports of convulsions that may have been due to concomitant use of quinolones and NSAIDs.

Pregnancy and Lactation

Inhibition of prostaglandin synthesis may have a negative impact on pregnancy and/or embryofetal development. Data from epidemiological studies suggest an elevated risk of miscarriage, and of cardiac malformation and gastroschisis, following use of a prostaglandin synthetase inhibitor during early pregnancy. The risk is assumed to rise with the dose and the duration of therapy.
In animals, administration of a prostaglandin synthetase inhibitor has been shown to result in increased pre-implantation and post-implantation loss and embryofetal lethality. In addition, increased incidences of various malformations, including cardiovascular malformations, have been reported in animals given a prostaglandin synthetase inhibitor during organogenesis.
During the first and second trimesters of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first or second trimesters of pregnancy, the dose should be kept as low – and the duration of treatment as short – as possible.
Diclofenac is contraindicated during the third trimester of pregnancy. All prostaglandin synthetase inhibitors may:

- expose the fetus to the following risks:
  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus, and pulmonary hypertension).
  - renal dysfunction, which may progress to renal failure with oligohydramnios.
- expose the mother and child to the following risks:
  - possible prolongation of bleeding time, inhibition of platelet aggregation even at very low doses.
  - inhibition of uterine contractions, resulting in delayed or prolonged labour.

Lactation
As with other NSAIDs, small amounts of diclofenac pass into the breast milk. Therefore, in order to avoid adverse effects in the infant, Voltfast should not be used by breastfeeding women. If treatment is essential, the infant should be switched to bottle feeding.

Fertility
Diclofenac may impair female fertility and is therefore not recommended in women attempting to conceive. Consideration should be given to withdrawing diclofenac in women who have difficulty becoming pregnant, or in those being tested for infertility.

Effects on ability to drive and use machines

Patients experiencing visual disturbances, light-headedness, dizziness, drowsiness or other central nervous system disturbances while taking Voltfast should refrain from driving or using machines.

Adverse effects

The following adverse effects include those reported with Voltfast and/or other dosage forms of diclofenac during either short-term or long-term use.

Frequency
Very common (> 1/10), common (> 1/100 to < 1/10), uncommon (> 1/1000 to < 1/100), rare (> 1/10 000 to < 1/1000), very rare (< 1/10 000).

Blood and lymphatic system disorders
Very rare: Thrombocytopenia, leucopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.

Immune system disorders
Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare: Angioedema (including facial oedema).

Psychiatric disorders
Very rare: Disorientation, depression, insomnia, nightmares, irritability, psychotic disorders.

Nervous system disorders
Common: Headache, light-headedness.
Rare: Drowsiness.
Very rare: Paraesthesia, memory impairment, convulsions, anxiety, tremor, aseptic meningitis, dysgeusia, cerebrovascular accidents.

Eye disorders
Very rare: Visual disturbances, blurred vision, diplopia.

Ear and labyrinth disorders
Common: Vertigo.
Very rare: Tinnitus, hearing impairment.

Cardiac disorders
Very rare: Palpitations, chest pain, heart failure, myocardial infarction, hypertension.

Vascular disorders
Very rare: Vasculitis.

Respiratory disorders
Rare: Asthma (including dyspnoea).
Very rare: Pneumonitis.

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, loss of appetite.
Rare: Gastritis, gastrointestinal bleeding, haematemesis, melaena, haemorrhagic diarrhoea, gastrointestinal ulcer (with or without bleeding or perforation).
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.

Hepatobiliary disorders
Common: Elevated transaminases.
Rare: Hepatitis, jaundice, hepatic dysfunction.
Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure.

Skin disorders
Common: Rash.
Rare: Urticaria.
Very rare: Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), exfoliative dermatitis, hair loss, photosensitivity reactions, purpura, allergic purpura, pruritus.

Renal and urinary disorders
Common: Fluid retention, oedema, hypertension.
Very rare: Acute renal insufficiency, haematuria, proteinuria, interstitial nephritis, nephrotic syndrome, renal papillary necrosis.

Clinical studies and epidemiological data suggest that diclofenac, particularly at high doses (150 mg daily) and with prolonged use, may be associated with an elevated risk of arterial thromboembolic events (e.g. myocardial infarction or stroke; see **Warnings and Precautions**).

Overdose

Signs and symptoms
There is no typical clinical picture following diclofenac overdosage. Overdosage may cause symptoms such as vomiting, gastrointestinal bleeding, diarrhoea, light-headedness, tinnitus or convulsions. Acute renal failure and liver damage are possible in the event of severe intoxication.

Therapeutic measures
Management of acute intoxication 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 disorders and respiratory depression.
Specific measures such as forced diuresis, dialysis or haemoperfusion are unlikely to be helpful in

accelerating the elimination of NSAIDs, including diclofenac, because of their 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.

Properties and Actions

ATC code: M01AB05

Mechanism of action

Diclofenac, the active substance of Voltfast, is a nonsteroidal compound with analgesic, anti-inflammatory and antipyretic properties.

Inhibition of prostaglandin biosynthesis has been demonstrated experimentally and is considered fundamental to the mechanism of action of diclofenac. Prostaglandins play a major causative role in inflammation, pain and fever.

In vitro, at concentrations equivalent to those attained in humans, diclofenac does not suppress proteoglycan biosynthesis in cartilage.

Clinical efficacy

On account of its rapid absorption, Voltfast is suitable for the treatment of acute painful and inflammatory conditions in which a rapid onset of action (within 30 minutes) is desired.

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

In addition, the active substance can relieve the pain, and reduce bleeding, in primary dysmenorrhoea. Diclofenac has also been shown to exert an analgesic effect in other moderately and severely painful states.

In migraine attacks, Voltfast has been shown to be effective in relieving headache and the nausea and vomiting that accompany it.

Pharmacokinetics

Absorption

Diclofenac is absorbed rapidly and completely from the diclofenac potassium powder. Absorption begins immediately after administration, and the amount absorbed corresponds to that absorbed from an equivalent dose of diclofenac sodium administered in the form of gastro-resistant tablets. Mean peak plasma concentrations of 5.5 µmol/litre are attained within 5–20 minutes of administration of the contents of a 50 mg sachet. Ingestion of the product together with food has no effect on the amount of diclofenac absorbed, but may slightly delay the onset – and reduce the rate – of absorption.

Distribution

Diclofenac is 99.7% bound to serum proteins, mainly albumin (99.4%).

The apparent volume of distribution has been calculated at 0.12–0.17 litres/kg.

Diclofenac enters the synovial fluid, where peak concentrations are measured 2–4 hours after peak plasma levels are reached. The apparent half-life of elimination from synovial fluid is 3-6 hours. Concentrations of active substance in the synovial fluid are already higher than those in the plasma two hours after peak plasma concentrations are attained, and they remain higher for up to 12 hours.

Metabolism

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

Elimination

Total body clearance of diclofenac from the plasma is 263 ± 56 ml/minute (mean ± SD). The terminal half-life is 1–2 hours.

Four of the metabolites, including the two that are active, also have short half-lives of 1-3 hours. The virtually inactive metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a much longer half-life.

About 60% of the dose is excreted in the urine as metabolites, as against less than 1% as unchanged substance. The rest of the dose is eliminated as metabolites via the bile in the faeces.

Pharmacokinetics in special patient populations

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

In patients with renal impairment, the drug's single-dose kinetics do not suggest that there is any accumulation of unchanged active substance with the usual dosage regimen. In patients with a creatinine clearance of less than 10 ml/minute, theoretical steady-state plasma levels of the metabolites are about 4 times higher than in normal subjects. Nonetheless, the metabolites are ultimately eliminated via the bile.

In patients with hepatic impairment (chronic hepatitis or compensated cirrhosis), the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

Preclinical data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no evidence of any specific hazard for humans given the designated therapeutic doses. There is no evidence that diclofenac is teratogenic in mice, rats or rabbits.

Diclofenac had no effect on the fertility of parental rats. The prenatal, perinatal and postnatal development of the offspring were not impaired.

Other information

Shelf-life

See folding box

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

See folding box

Pack sizes

Country specific packs

Manufacturer

See folding box

Information last revised

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Approval date (text)

30 March 2010

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists