Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Voltfast Sachets 50mg Powder for Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is potassium [o-[(2,6-dichlorophenyl)-amino]-phenyl-acetate (diclofenac potassium).

One sachet contains 50 mg of diclofenac potassium.

One sachet also contains 50mg aspartame (E951).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution.
White to light yellow powder for oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short-term treatment of all grades of pain and inflammation in the following acute conditions:
● Post traumatic pain, inflammation and swelling, e.g. due to sprains.
● Acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder).
● Post-operative pain, inflammation and swelling, e.g. following dental or orthopaedic surgery.
● Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis and associated menorrhagia.
● Migraine attacks.
● 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. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

The contents of the sachet should be dissolved with stirring in a glass of natural (non-carbonated) 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.

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

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

In migraine an initial dose of 50mg 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 50mg may be taken. If needed, further doses of 50mg may be taken at intervals of 4-6 hours, not exceeding a total dose of 200mg per day.

Children and adolescents
Voltfast 50mg 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 12.5mg are available.

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

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

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

Older people (Patients aged 65 or above)
Although the pharmacokinetics of Votlfast are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should be used with particular caution in frail elderly patients or those with a low body weight. In particular, it is recommended that the lowest effective dosage be used in these patients (see Section 4.4). Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or if intolerance occurs.

Renal impairment
Diclofenac is contraindicated in patients with severe renal impairment (see section 4.3).
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 diclofenac to patients with mild to moderate renal impairment (see section 4.3 and 4.4).

Hepatic impairment
Diclofenac is contraindicated in patients with severe hepatic impairment (see section 4.3).
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 diclofenac to patients with mild to moderate hepatic impairment (see section 4.3 and 4.4).

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients listed in Section 6.1
- 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 Pregnancy and lactation)
- Hepatic failure
- Chronic Kidney Disease Grade 5 (GFR <15 mL/min./1.73m^2)
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- 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 (see Section 4.4 and Section 4.8).

4.4 Special warnings and precautions for use

General
Undesirable effects may be minimised by using the lowest effective dose for the shortest possible duration necessary to control symptoms (see section 4.2 Posology and GI and cardiovascular risks below).
The concomitant use of Nigfast 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.
Caution is indicated in the elderly on basic medical grounds. especially used in frail elderly patients or those with a low body weight.
Like other NSAIDs, Nigfast may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Nigfast contains a source of phenylalanine and may be therefore harmful for patients with phenylketonuria.
The use of diclofenac potassium 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 diclofenac potassium should be considered.
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.

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. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2 Posology and method of administration). When gastrointestinal bleeding or ulceration occurs in patients receiving Nigfast, the medicinal product should be withdrawn.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Nigfast 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, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3 Contra-indications) The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see Section 4.2)

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.

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 (see below and section 4.5 Interactions with other medicinal products and other forms of intraction).

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, anti-platelet agents such as aspirin or selective serotonin-reuptake inhibitors (see section 4.5 Interaction with other medicinal products and other forme 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 4.8 Undesirable effects).
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.

Hepatic effects
Close medical surveillance is required when prescribing Nigfast 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 diclofenac, 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 etc.), Nigfast should be discontinued. Hepatitis may occur with use of diclofenac , without prodromal symptoms.
Caution is called for when using diclofenac 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 Nigfast in such cases. Discontinuation of therapy is normally followed by a recovery to the pre-treatment state.

Skin Effects
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 Nigfast (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. Nigfast should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Cardiovascular and cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or congestive heart failure (NYHA-1) as fluid retention and oedema have been reported in association with NSAID therapy.
Clinical trial and epidemiological data suggest that the use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
Patients with congestive heart failure (NYHA-1), and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.
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.
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.

Haematological effects
Use of Nigfast is recommended only for short-term treatment. If, however, Nigfast is used for a prolonged period, monitoring of the blood count is recommended, as with other NSAIDs.
Like other NSAIDs, Nigfast may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

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.

4.5 Interaction with other medicinal products and other forms of interactions

(Including interactions observed with other dosage forms of diclofenac potassium and diclofenac sodium)

Observed Interactions to be considered:
CYP_2C_9 inhibitors: Caution is recommended when co-prescribing diclofenac with CYP_2C_9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac.
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.

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

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

Diuretics and antihypertensive drugs: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive drugs (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 be 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: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin 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.

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 risk of gastrointestinal bleeding (see Section 4.4 special warnings and precautions for use).

Anticoagulant and anti-platlet agents: **Caution is recommended since concomitant administration could increase the risk of bleeding see section 4.4.** Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are also 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.

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.

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
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. During the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac 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.

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;

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, diclofenac is contraindicated during the third trimester of pregnancy.

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

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.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo, somnolence or other central nervous system disturbances while taking Voltfast, including visual disturbances, should not drive or operate machines.

4.8 Undesirable effects

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 1) are listed by MedRA system order 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).

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4 Special warnings and precautions for use). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of coilitis and Crohn's disease (see section 4.4 Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

The following table of 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 1

Blood and lymphatic system disorders	
Very rare:	Thrombocytopenia, leucopenia, anemia (including haemolytic anemia 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 reactions.
Nervous system disorders	
Common:	Headache, dizziness.
Rare:	Somnolence.
Very rare:	Paresthesias, memory impairment, convulsions, anxiety, tremor,

	meningitis aseptic, dysgeusia, cerebrovascular accident.
Eye disorders	
Very rare:	Visual impairment (blurred vision, diplopia).
Ear and labyrinth disorders	
Common:	Vertigo.
Very rare:	Tinnitus, hearing impaired.
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/bronchospasm (including dyspnea).
Very rare:	Pneumonitis.
Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, decreased appetite.
Rare:	Gastritis, gastrointestinal hemorrhage, hematemesis, melena, diarrhea hemorrhagic, 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 (including ulcerative stomatitis), glossitis, esophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Not known:	Ischemic colitis
Hepatobiliary disorders	
Common:	Transaminases increased.
Rare:	Hepatitis with or without jaundice, liver disorder.
Very rare:	Hepatitis fulminant, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common:	Rash.
Rare	Urticaria.
Very rare:	Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, alopecia, photosensitivity reaction, Henoch-Schonlein purpura, allergic purpura], pruritus.
Renal and urinary disorders	
Very rare:	Acute kidney injury (acute renal failure), haematuria, proteinuria, nephritic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare:	Edema.

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

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 doses (150 mg daily) and in long term treatment (see section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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.

Therapeutic measures
Management of acute poisoning with NSAIDs including diclofenac consists essentially 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 haemoperfusion are probably unlikely to be helpful in accelerating the elimination of NSAIDs including diclofenac because of their high protein binding rate 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).

Mechanism of action

Voltfast contains the potassium salt of diclofenac, a non-steroidal compound with pronounced analgesic, anti-inflammatory, and antipyretic properties.

Voltfast has a rapid onset of action, which makes it particularly suitable for the treatment of acute painful and inflammatory conditions. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered to be fundamental to its mechanism of action. 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.

Pharmacodynamic effects

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 oedema. Clinical studies have also revealed that in primary dysmenorrhoea the active substance is capable of relieving the pain and reducing the extent of bleeding. In migraine attacks Voltfast has been shown to be effective in relieving the headache and in improving the accompanying symptoms nausea and vomiting.

There is limited clinical trial experience of the use of diclofenac in Juvenile Rheumatoid Arthritis (JRA)/Juvenile Idiopathic Arthritis (JIA) paediatric patients. In a randomized, double-blind, 2-week, parallel group study in children aged 3-15 years with JRA/JIA, the efficacy and safety of daily 2-3 mg/kg BW diclofenac was compared with acetylsalicylic acid (ASS, 50-100 mg/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 randomized, double-blind, 6-week, parallel group study in children aged 4-15 years with JRA/JIA, the efficacy of diclofenac (daily dose 2-3 mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3mg/kg BW, n=23).

5.2 Pharmacokinetic properties

Absorption

Diclofenac is rapidly and completely absorbed from diclofenac potassium. Mean peak plasma concentrations of 5.5 micromol/L are attained after 5-20 minutes after ingestion of one sachet of 50mg.

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. The amount absorbed is in linear proportion to the size of the dose.

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.

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

Distribution
99.7% of diclofenac binds to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12-0.17 L/kg.

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after peak plasma values have been reached. The apparent half-life for elimination from the synovial fluid is 3-6 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.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

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

Elimination
Total systemic clearance of diclofenac from plasma is 263 ± 56 mL/min (mean value ± SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 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.

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

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of less than <10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

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

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 preclinical animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

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

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors (see sections 4.3 Contraindications and 4.6 Fertility, pregnancy and lactation).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium hydrogen carbonate
Mannitol
Aspartame
Saccharin sodium
Glyceryl dibehenate
Mint flavour
Anise flavour

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with anything other than water.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Sachet consisting of coupled paper/aluminium/polyethylene, hermetically sealed in four directions. Three sachets are packaged in one carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Wisdom Pharmaceutical Technology Co Limited
Wilton Park House
Wilton Place
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2308/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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