SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eeze 25 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg diclofenac potassium.

Excipients:
Each tablet contains 27.2 mg lactose monohydrate.
For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Pink, round, biconvex tablets (6 mm diam).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute pain conditions in adults, such as headache, including episodic attacks of migraine, toothache, joint or muscle pain, back pain and primary dysmenorrhoea.
Symptomatic, short-term treatment in children and adolescents of pain related to inflammatory infections of the ear, nose or throat, e.g. pharyngotonsillitis, otitis (see 4.4).
Symptomatic, short-term treatment in children and adolescents of acute post-operative pain after minor surgery.

4.2 Posology and method of administration

Treatment should be initiated at the lowest effective dose. The dose can be subsequently adjusted with respect to the response to therapy and any undesirable effects. The aim should be to administer a low dose during long-term treatment. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see 4.4).

Adults and adolescents over 16 years:
For migraine: Initially 50 mg at the first sign of an attack. A further 50 mg to be given if relief is not achieved within 2 hours. This can be repeated at intervals of 4–6 hours, up to a maximum daily dose of 150 mg.
Other pain: 25–50 mg every 4–6 hours, as required. The highest recommended daily dose is 150 mg.

The rate of diclofenac absorption is reduced if Eeze is taken with food. It is not advisable to take the tablets with food or directly after a meal.

Impaired hepatic or renal function:
No dosage reduction appears to be necessary for patients with mild to moderate hepatic or renal impairment. Diclofenac is contraindicated in patients with severe hepatic or renal impairment (see 4.3). Patients with moderate renal or hepatic impairment should be carefully monitored. The lowest effective dose should be given.

Elderly patients:
The aim should be to administer the lowest effective dose (see 4.4).

Children and adolescents:
Children ages 9 years (min. 35 kg BW) or over and adolescents should be given up to 2 mg/kg body weight per day in 3 divided doses, depending on the severity of the disorder.

Body weight (corresponding age)	*Dosage forms*	*Single dose*	*Maximum daily dose*
35-44 kg BW (9-11 yr)	25 mg tablets	25 mg	25 mg x3
45-55 kg BW (12-16 yr)	25 mg tablets	25 mg	25 mg x3-4

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
  Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Hepatic porphyria.
- Conditions giving an increased tendency to bleeding.
- Last trimester of pregnancy (see 4.6).
- Severe hepatic or renal failure (see 4.4).
- 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), Diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs

4.4 Special warnings and precautions for use

General
There is a clear correlation between the dose and serious gastrointestinal side effects. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see 4.2, and GI and cardiovascular risks below).

The use of Eeze with concomitant 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. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

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

Eeze contains lactose. Patients with rare hereditary problems of: galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Prolonged use of any type of painkiller for headaches can make the headache worse. If this situation is experienced or suspected, treatment should be discontinued. The diagnosis of Medication Overuse Headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Eeze in case of varicella.

Patients with gastrointestinal problems or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see 4.8) as well as patients with ulcerous colitis, Crohn’s disease, impaired hepatic function, SLE, haematopoiesis or coagulation disorders should be kept under careful monitoring when treated with diclofenac.

Patients who are being treated with oral anticoagulants or antidiabetics should be monitored with respect to overdose in the event of concomitant treatment with diclofenac. Laboratory tests should be carried out in order to check that the desired effect of anticoagulants is maintained. Isolated cases of hypoglycaemia and of hyperglycaemic effects that require dose adjustment of antidiabetic agents have been reported.

NSAIDs can inhibit the diuretic effect and enhance the potassium-sparing effect of diuretics, which makes it necessary to check serum potassium levels.

Paediatric population
In children and adolescents with pain related to infections with an inflammatory component in the ear, nose and throat regions, the underlying disease should be treated with anti-infective basic therapy, as therapeutically appropriate. Fever alone without inflammatory component is not an indication.

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

If gastrointestinal bleeding or ulceration occurs in patients receiving Diclofenac, the medicinal product should be withdrawn.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Diclofenac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see 4.8). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with 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.
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 4.5).

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 4.8).

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

As with other analgesics, the following applies: if patients with acute abdominal pain are repeatedly given pain relief, this can modify or disguise the pattern of symptoms of associated complications such as perforation.

Hepatic effects
Close medical surveillance is required when prescribing Diclofenac 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), Diclofenac 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 4.3). Monitoring of renal function is recommended as a precautionary measure when using Diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.
Cases of acute renal failure after intake of tenofovir disoproxil fumarate have been reported in patients treated with high dose or multiple non-steroidal anti-inflammatory (NSAIDs) drugs and with risk factors for renal dysfunction. If tenofovir disoproxil fumarate is co-administered with an NSAID, renal function should be monitored adequately.

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 NSAIDSs (see 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Eeze 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 hypertension and/or a history of mild congestive heart failure (NYHA I), as fluid retention and oedema have been reported in association with NSAID therapy.

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 short 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.

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

Like other NSAIDs, Diclofenac 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 interaction

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

Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Heparin (parenteral administration): An increased risk of bleeding (inhibition of platelet function and increased gastrointestinal side effects of NSAIDs).

Pentoxifylline: Increased risk of bleeding: increased clinical monitoring and check of bleeding times are recommended.

Zidovudine: Increased risk of bleeding (haemarthrosis and haematoma) in HIV-positive haemophiliac patients.

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

Angiotensin II antagonists: NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administrated with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Other NSAIDs: Concomitant systemic administration of other NSAIDs should in general be avoided due to the increased risk of undesirable effects.

Quinolones: Convulsions may occur as a consequence of interactions between quinolones and NSAIDs. They can occur in patients with or without a previous history of epilepsy or convulsions. For this reason care should be taken when considering the administration of quinolones to patients already taking NSAIDs.

Oral 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.

Corticosteroids: Concomitant treatment with diclofenac and corticosteroids can increase the risk of gastrointestinal bleeding (see section 4.4).

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.

Lithium: Diclofenac reduces the renal clearance of lithium by about 20% and thus increases serum lithium levels. It may be necessary to adjust the lithium dose. The combination should be avoided unless frequent checks of serum lithium can be carried out at the time of the introduction and the discontinuation of the treatment.

Ciclosporin and tacrolimus: A relatively high frequency of nephrotoxicity (increasing levels of serum creatinine) with increasing blood pressure has been observed during concomitant treatment with diclofenac and ciclosporin (for rheumatoid arthritis). It is probable that the risk is present during concomitant treatment with tacrolimus. Furthermore, the plasma concentration of diclofenac doubled following a single oral dose of ciclosporin during ongoing diclofenac treatment. Combination treatment should be carried out with care. The dose of diclofenac should be halved if combination treatment is given.

Digoxin: Trials in healthy subjects show that the introduction of diclofenac in persons being treated with digoxin results in increased plasma levels of digoxin. If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

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.

Tenofovir
Cases of acute renal failure after intake of tenofovir disoproxil fumarate have been reported in patients treated with high dose or multiple non-steroidal anti-inflammatory (NSAIDs) drugs and with risk factors for renal dysfunction. If tenofovir disoproxil fumarate is co-administered with an NSAID, renal function should be monitored adequately.

Drugs that inhibit or induce the enzyme CYP2C9: The metabolism of diclofenac is catalysed by the enzyme CYP2C9. Concomitant treatment with drugs (such as fluconazole, sulfinpyrazone and voriconazole) that inhibit this enzyme probably lead to higher concentrations of diclofenac in plasma. Drugs such as rifampicin, carbamazepine and barbiturates, which induce CYP2C9 activity, can reduce the plasma concentration of diclofenac to subtherapeutic levels. Diazepam, which is metabolised via CYP2C19, increases the plasma concentration of diclofenac by 50–100%. Voriconazole, which is metabolised via

CYP2C19 increased Cmax and AUC diclofenac (a single dose of 50 mg) with 114 % and 78 %, respectively. Dose adjustment of the NSAID may be necessary.

The rate of absorption of diclofenac is reduced when Eeze is taken with meals. It is therefore not advisable for the tablets to be taken with or immediately after meals.

Paediatric population
Interaction studies have only been performed in adults.

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 postimplantation loss and embryo-fetal 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, Eeze should not be given unless clearly necessary. If Eeze 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 fetus 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 after very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Eeze is contraindicated during the third trimester of pregnancy (see 4.3 and 4.4).

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

Fertility
As with other NSAIDs, the use of Diclofenac 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 should be considered.

4.7 Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking Diclofenac, should refrain from driving or using machines.

4.8 Undesirable effects

Gastrointestinal problems can occur at the start of treatment in approximately 10% of patients. These undesirable effects normally disappear after a few days, even if treatment is continued. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Such problems can occur at any time during treatment, with or without warning symptoms and with or without previous history of disease.
Diclofenac temporarily inhibits platelet aggregation, which may lead to increased risks in patients with various bleeding conditions.
Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Exceptionally, occurrence of serious cutaneous and soft tissues infectious complications during varicella.

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

The following frequencies are used for the description of the occurrence of adverse reactions: Very common (>1/10), Common (>1/100, <1/10), Uncommon (>1/1000, <1/100), Rare (>1/10,000, <1/1000), Very rare (<1/10,000), Frequency not known (cannot be estimated from the available data).

The following undesirable effects include those reported with either short-term or long-term use.

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), Agranulocytosis.
Immune system disorders	
Rare Very rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders	
Common Rare Very rare	Headache, dizziness. Somnolence, disturbances of sensation. Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Ear and labyrinth disorders	
Common Very rare	Vertigo. Tinnitus, hearing impaired.
Cardiac disorders	
Very rare Not known	Palpitations, chest pain, cardiac failure, myocardial infarction. Kounis syndrome
Vascular disorders	
Very rare	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Uncommon Rare Very rare	Bronchospasm Asthma (including dyspnoea). Pneumonitis.
Gastrointestinal disorders	
Common Rare Very rare	Epigastric pain, nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia. Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation). Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, Stomatitis (including aphthous and ulcerative stomatitis), glossitis, oesophageal disorder, oesophageal lesions, diaphragm-like intestinal strictures, pancreatitis.
Not known	Ischaemic colitis
Hepatobiliary disorders	
Common Rare Very rare	Transaminases increased. Hepatitis, jaundice, liver disorder. Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common Rare Very rare	Rash. Urticaria. Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders	

Rare Very rare	Acute renal insufficiency Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Uncommon Rare	Tiredness Oedema, impotence (causative relation is unclear)

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 the national reporting system (To be completed nationally).

4.9 Overdose

Doses more than 300 mg could be toxic.
Administration of 50 mg to children aged 1–3 years gave no or only mild intoxication. Administration of 150 mg followed by activated charcoal tablets to a 2-year-old gave mild intoxication. Administration of 325 mg to an adult gave moderate intoxication. Administration of 2.8 g during one week resulted in intestinal perforation of an adult, 2 g to an adult gave renal effects.
Reversible bone marrow necrosis has been reported due to overdose of diclofenac given intramuscularly for renal colic in a dose of 75mg repeatedly with 30-minutes intervals for 12 doses, a total dose of 900mg.

Symptoms: There is no typical clinical picture resulting from diclofenac over dosage. Over dosage 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, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.
Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory/antirheumatic drug, NSAID, ATC code: M01AB05

Eeze contains the potassium salt of diclofenac, a non-steroidal substance with anti-inflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin synthesis has been shown experimentally to be an important component of the mechanism of action. Prostaglandins play a prominent role in inflammation, pain and fever. This means that diclofenac also inhibits platelet aggregation. Diclofenac exhibits anti-inflammatory and analgesic properties in rheumatic diseases, clinically manifested as relief of symptoms such as pain when resting and in motion, early morning stiffness and swollen joints. These properties are also manifested as improvement in function.
Diclofenac has been shown in clinical trials to relieve pain and reduce blood volumes in primary dysmenorrhoea.
Diclofenac inhibits renal prostaglandin synthesis. This effect is not significant in patients with normal renal function. The inhibition of prostaglandin synthesis can, however, lead to acute renal insufficiency, fluid retention and heart failure in patients with chronic renal, cardiac or liver insufficiency and with conditions that change plasma volume (see 4.3).

There is limited clinical trial experience of the use of diclofenac in JRA/JIA paediatric patients. In a randomised, double-blind, 2-week, parallel group study in children aged 3-15 years with 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 randomised, 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 2-3 mg/kg BW, n=23).

5.2 Pharmacokinetic properties

Absorption
A maximum plasma concentration of approximately 1 microgram/ml (approximately 4 micromol/l) is reached 20–60 min after ingestion of a 50 mg tablet. The rate of absorption is reduced if the tablet is taken with food.

Distribution
The serum protein binding of diclofenac is 99.7% and the drug is predominantly bound to albumin (99.4%).
A maximum concentration of diclofenac is reached in the synovial fluid 2–4 hours after the peak plasma concentration is reached. The half-life in the synovial fluid is 3–6 hours. The concentration of active substance is higher in the synovial fluid than in the plasma 4–6 hours after ingestion, remaining so for up to 12 hours.

Biotransformation
The biotransformation of diclofenac comprises single and multiple hydroxylation and glucuronidation.

Elimination

The active substance is eliminated from plasma with a total clearance of 263 ±56 ml/min. The half-life is 1–2 hours. Approximately 60% of the administered dose is excreted in the urine in the form of metabolites and less than 1% is excreted as unchanged substance. The remainder of the dose is excreted as metabolite in bile and faeces.
Pharmacokinetic properties are unchanged following repeated administration. There is no accumulation at the recommended dosage interval.

Special patient groups
Elderly patients
The age of the patient has no effect on the absorption, metabolism or excretion of diclofenac.

Impaired renal function
No accumulation of unmetabolised active substance is seen following single-dose administration to patients with impaired renal function. The theoretical steady-state plasma level of the metabolites is approximately four times higher in patients with a creatinine clearance less than 10 ml/min than in healthy subjects (see 4.2, 4.3 and 4.4).

Impaired hepatic function
The kinetics and metabolism of diclofenac are the same for patients with hepatic impairment (chronic hepatitis, non-decompensated cirrhosis) as for patients with normal hepatic function (see 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

No additional preclinical information that is considered to be significant for clinical safety is available, apart from the information given in other parts of this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Magnesium stearate
Sodium starch glycolate
Hypromellose
Macrogol
Talc
Simethicone
Sorbic acid (E200)
Benzoic acid (E210)
Macrogol palmitate
Macrogol stearate
Monoglycerides and diglycerides
Octamethylcyclotetrasiloxane
Titanium dioxide (E171)

Red iron oxide (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packaging of PVC/PVDC/aluminium.
6, 10, 12, 18, 20, 30, 40, 80, 100 and 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Meda OTC AB
Box 906,
170 09 Solna

8. MARKETING AUTHORISATION NUMBER(S)

25 mg: 19999

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 January 2006/29 May 2010

10. DATE OF REVISION OF THE TEXT

12 November 2019