SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diklotab 25 mg film-coated tablets
Diklotab 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg or 50 mg diclofenac potassium.

Excipients:

Tablets 25 mg:	
Mannitol	58.2 mg
Potassium hydrogen carbonate	11.0 mg
Tablets 50 mg:	
Mannitol	116.4 mg
Potassium hydrogen carbonate	22.0 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Tablets 25 mg:
White, round, biconvex tablets approximately 6 mm diameter and thickness approx. 3 mm.

Tablets 50 mg:
White, round, biconvex tablets approximately 7 mm diameter and thickness approx. 5 mm.

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 section 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 assumed effective dose. The dose can subsequently be adjusted according to the therapeutic response and any undesirable effects. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control the symptoms (see section 4.4). During long-term treatment the aim should be to administer a low dose.

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.

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)	Single dose	Maximum daily dose
35-44 kg BW (9-11 yr)	25 mg	25 mg x3
45-55 kg BW (12-16 yr)	25 mg	25 mg x3-4

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

Impaired hepatic function:
Diklotab is contraindicated in patients with severe hepatic impairment. Patients with mild to moderate hepatic impairment, see Section 4.4 under Special warnings and precautions for use / Hepatic effects.

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 NSAID therapy.
- Active or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Last trimester of pregnancy (see 4.6).
- Conditions giving an increased bleeding tendency.
- Severe hepatic, renal or cardiac failure.
- Hepatic porphyria.
- Severe renal impairment (glomerular filtration rate < 30 ml/min).
- 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
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 concomitant use of Diklotab 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. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight. Elderly patients have an increased risk of adverse reactions to NSAIDs especially gastrointestinal

bleeding and perforation which may be fatal. Elderly patients are also more likely to suffer from impaired renal, heart or liver function.

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

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

For OTC products only:
Low-dose, short-term, oral diclofenac forms with headache indication:
Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

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 Diklotab, 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 Diklotab 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).

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

As for other NSAID's, severe hepatic damage has been reported during treatment with diclofenac (see section 4.8).

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Diklotab, 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), Diklotab should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using Diklotab in patients with hepatic porphyria, since it may trigger an attack.

Treatment with NSAIDs in patients with chronic hepatic disease should be avoided where possible due to the increased risk of gastrointestinal bleeding.

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 e.g. cyclosporine, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see 4.3 and 5.2). Monitoring of renal function is recommended as a precautionary measure when using Diklotab in such cases. Discontinuation of therapy is usually followed by 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 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.

Diklotab should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue 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 Diklotab in cases of varicella.

Cardiovascular and cerebrovascular effects
For OTC products only:
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that 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). Available data do not suggest an increased risk with use of low dose diclofenac (daily dose 25-75 mg up to 5 days).

For POM products only:
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trials and epidemiological data suggest that use of diclofenac, particularly at a high dose (150 mg daily) and in long term treatment, may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke).

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, and smoking).

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. This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Other
As with other NSAIDs, Diklotab can, in rare cases, cause allergic reactions including anaphylactic/anaphylactoid reactions (see 4.8).

As with other NSAIDs, the pharmacodynamic properties of diclofenac mean that it can mask the signs or symptoms of infection.

Patients with SLE should be carefully monitored during treatment with diclofenac.

Patients who are being treated with oral anticoagulants or antidiabetics should be monitored during concomitant treatment with diclofenac. Laboratory tests should be carried out to ensure 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 monitor serum potassium levels.

Use of diclofenac can reduce fertility and it is for this reason not recommended in women attempting to conceive. This is true for all medicinal products that inhibit the synthesis of cyclo-oxygenase and prostaglandins. The effect is reversible and ends when the use of these types of medicinal products is discontinued.

Children and adolescents
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.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

Pharmacodynamic interactions

Anticoagulants and antiplatelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see 4.4). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin II-antagonists and 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).

Other NSAIDs: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see 4.4).

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see 4.4).

Quinolone antibacterials: There have been isolated reports of convulsions which may have been due to concomitant use of 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.

Pharmacokinetic interactions
Effects of diclofenac on the pharmacokinetics of other drugs:

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Concomitant treatment with diclofenac and high doses of methotrexate should be avoided. Care should be observed during concomitant low-dose methotrexate treatment, and patients should be monitored with respect to methotrexate-related toxicity. 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. Monitoring of lithium concentrations is recommended.

Ciclosporin and tacrolimus: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. It is probable that the risk is present during concomitant treatment with tacrolimus. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Digoxin:
The introduction of diclofenac in persons being treated with digoxin can result in increased plasma levels 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.

Effects of other drugs on the pharmacokinetics of diclofenac:
Drugs that inhibit or induce the enzyme CYP2C9: The metabolism of diclofenac is catalysed by the enzyme CYP2C9. Concomitant treatment with drugs that inhibit this enzyme (such as fluconazole, sulfinpyrazone and voriconazole) probably leads to higher plasma concentrations of diclofenac. Drugs which induce CYP2C9 activity such as rifampicin, carbamazepine and barbiturates, 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.

Colestipol and cholestyramine: Concomitant administration of diclofenac with colestipol or cholestyramine reduces the absorption of diclofenac by about 30% (colestipol) and 60% (cholestyramine). 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 pregnancy and/or embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage, cardiac malformations and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from under 1% 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-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 trimesters of pregnancy, Diklotab should not be given unless clearly necessary. If Diklotab is used by a woman attempting to conceive, or during the first and second trimesters 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 due to an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Diklotab is contraindicated during the third trimester of pregnancy.

Lactation
Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, Diklotab 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 disturbances are the commonest reported undesirable effects. Approximately 10% of patients experience such effects at the start of treatment. 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 a previous history of disease.
Diclofenac causes temporary inhibition of platelet aggregation which may lead to increased risks in patients with various bleeding conditions.
Exceptionally, occurrence of serious cutaneous and soft tissues infectious complications occur during varicella.

The adverse reactions in the table are ranked under heading of frequency, the most frequent first, using the following convention: 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); Not known: cannot be estimated from the available data.

The table includes undesirable effects reported from both short-term and 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. 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	Palpitations, chest pain, cardiac failure,

	myocardial infarction.
Vascular disorders	
Very rare	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Uncommon Rare Very rare	Broncospasm Asthma (including dyspnoea). Pneumonitis.
Gastrointestinal disorders	
Common Rare Very rare	Epigastric pain, nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, flatulence, anorexia. Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation). Diaphragm-like intestinal strictures. Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, Stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder. Pancreatitis.
Hepatobiliary disorders	
Common Rare Very rare	Transaminases increased (AST, ALT). 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	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
Reproductive system and breast disorders	
Rare	Impotence (causative relationship doubtful)
General disorders and administration site conditions	
Rare	Oedema

Clinical trial and epidemiological data suggest that 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) (see 4.4).

4.9 Overdose

Toxicity
Administration of 50 - 100 mg to children aged 1–3 years gave no or only mild intoxication. 150 mg followed by activated charcoal to a 2-year-old gave mild intoxication. 300 mg – 3 g to adults usually

only give mild intoxication. 2.8 g given during one week caused intestinal perforation in 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 75 mg repeated with 30-minutes intervals for 12 doses, a total dose of 900 mg.

Symptoms
There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as nausea, vomiting, gastrointestinal haemorrhage, diarrhoea, abdominal pain, dizziness, somnolence, headache, tinnitus, anxiety, hallucinations, renal effects, in rare cases hepatic effects, a tendency to oedema, possible metabolic acidosis 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. Antacids as required, if necessary supplemented with sucralfate. Ensure efficient diuresis. Symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Diklotab contains the potassium salt of diclofenac, a non-steroidal substance with anti-inflammatory, analgesic and antipyretic properties.
Inhibition of prostaglandin synthesis has in experimental studies been shown 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. In rheumatic diseases diclofenac exhibits anti-inflammatory and analgesic properties, 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 an improvement in function.
Diclofenac has been shown in clinical trials to relieve pain and reduce the amount of menstrual blood loss 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 Section 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
Diklotab gives a lower t_{max} and a higher C_{max} compared with conventional diclofenac potassium tablets. In a comparative study, Diklotab 50 mg gave maximum plasma concentration after approximately 20 minutes. The absorption rate of diclofenac is reduced if the tablet is taken with food. It is therefore recommended that the tablets are not taken with, or directly after, a meal.
Distribution
The serum protein binding of diclofenac is 99.7% and the drug is predominantly bound to albumin (99.4%).
In synovial fluid maximum concentration of diclofenac occurs 2–4 hours after the peak plasma concentration was 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 metabolites 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 Sections 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 Sections 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

Tablet core

Potassium hydrogen carbonate
Mannitol
Sodium lauryl sulphate
Macrogol
Crospovidone
Magnesium stearate

Film coating
Hypromellose
Macrogol

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 polyamide/PVC/aluminium.

Tablets 25 mg: 10, 12, 18, 20, 30, 40, 80, 100 and 120 tablets.
Tablets 50 mg: 20, 30, 40, 50, 60, 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

Mimer Medical
Svärdvägen 3 B
182 33 Danderyd
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2010-08-27

10. DATE OF REVISION OF THE TEXT

2011-12-07