SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

*Diclofenac T ratiopharm 50 mg film-coated tablets*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diclofenac potassium, 50 mg

Excipient with known effect: lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Red-brown, round, biconvex film-coated tablet, diameter 11.1 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term symptomatic treatment of following acute conditions: Rheumatic conditions of soft tissue, posttraumatic and postoperative inflammation and pain, also in odontology, primary dysmenorrhea. Acute treatment of migraine with or without aura.

Diclofenac T ratiopharm tablets are not indicated for children under 16 years of age due to the amount of diclofenac in each tablet.

4.2 Posology and method of administration

**Posology**

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

*Adults and adolescents over 16 years:*

Generally the initial dose is 100-150 mg daily. In milder cases 75-100 mg/day is usually sufficient. The daily dose should be administrated in two to three divided doses.

*Primary dysmenorrhea:* The dose is 50 to 150 mg daily in two to three divided doses. The dosage should be adjusted individually. Initially, a smaller dose (50 to 100 mg/day) should be used and increased gradually during several cycles. The treatment is commenced at the appearance of the first symptoms and it is continued for a few days depending on how strong the symptoms are.

*Migraine:* In cases of migraine an initial 50 mg dose is administered at the first signs that an attack is imminent. In cases where pain relief in the 2 hours following administration is not sufficient a further 50 mg dose can be administered. If necessary supplementary doses of 50 mg can be administered at 4 to 6 hour intervals without exceeding a total dose of 200 mg per day.
**Paediatric population**

Diclofenac T ratiopharm tablets are not indicated for children under 16 years of age due to the amount of diclofenac in each tablet.

**Method of administration**

For oral use.
The tablets should be swallowed with a small amount of fluid preferably before meal.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active gastric or intestinal ulcer, bleeding or perforation.
- Ulcerative duodenal inflammation.
- 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).
- Severe hepatic or renal failure (see section 4.4).
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease
- Porphyria, haematopoetic disorders and diathesis.
- 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 section 4.2 and Gastrointestinal effects and Cardiovascular and cerebrovascular effects below).

The concomitant use of diclofenac 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 (see section 4.5).

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 (see section 4.8). Anaphylactic reactions of various grades may occur during diclofenac treatment in patients hypersensitive to acetylsalicylic acid or other NSAIDs. Therefore detailed anamnesis of the patient is necessary in order to discover possible earlier hypersensitivity reactions.

Like other NSAIDs, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties. So it should be used with caution in patients at risk of infection.

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 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 section 4.8). The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3). 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 (see below and section 4.5).

Patients with a history of GI toxicity, particularly when 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 systemic corticosteroids, anticoagulants such as warfarin, anti-platelet agents such as acetylsalicylic acid (ASA/aspirin) or selective serotonin-reuptake inhibitors (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving diclofenac, the treatment should be withdrawn.

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).

**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 section 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.
Use of diclofenac film-coated tablets is recommended only for short term treatment. During prolonged treatment with diclofenac, monitoring of the renal function is recommended.

**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 (see section 4.8). 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. Diclofenac 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 mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

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 dose (150 mg daily) and in long term treatment (see sections 4.3 and 4.8).

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.

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.

**Haematological effects**
Use of diclofenac film-coated tablets is recommended only for short term treatment. 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 and patients treated with anticoagulants should be carefully monitored (see section 4.5).

**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.

Caution is required if administrated to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to cause bronchospasm in such patients.

**Fertility**
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.

**Other warnings**
NSAIDs may decrease the diuretic effect and potentiate the effect of potassium-sparing diuretics, and therefore monitoring of serum potassium levels is necessary.

Diclofenac potassium is not indicated in for the management of hemiplegic, basilar or ophthalmoplegic migraine.

As with other treatments of migraine attack, it is necessary to exclude other, potentially serious, neurological conditions before treating the headache of patients without a previous diagnosis of migraine, or migraine patients presenting with atypical symptoms. It should be noted that migraineurs present an increased risk of certain cerebral vascular events (e.g. CVA or TIA).

The safety and efficacy of diclofenac potassium administered during the aura phase, before the headache phase of migraine, has not been established in clinical trials.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Clinical signs of overdose in these cases have not been detected.

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 and Angiotensin II antagonists) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients (with compromised renal function e.g. dehydrated 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.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4).

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs including cyclooxygenase-2 selective inhibitors or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4).

Anticoagulants and antiplatelet 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 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).

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.

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.

Quinolone antibacterials: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

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.

Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac metabolism.

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 gastrochisis 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-hydroamnios.

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.

**Breastfeeding**

Like other NSAIDs, diclofenac passes into the breast milk in small amounts (following oral doses of 150 mg/day [50 mg every 8 hours]). Therefore, diclofenac should not be administered during breastfeeding 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 (see section 4.4).

**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**

Adverse reactions (Table 1) 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 following undesirable effects include those reported with either short-term or long-term use.

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). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn’s disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).</td>
</tr>
<tr>
<td></td>
<td>Angioneurotic oedema (including face oedema).</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Disorientation, depression, insomnia,</td>
</tr>
</tbody>
</table>

Table 1
<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Headache, dizziness.</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Somnolence.</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Visual disturbance, vision blurred, diplopia.</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Vertigo.</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Tinnitus, hearing impaired.</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Palpitations, chest pain, cardiac failure, myocardial infarction.</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Hypertension, vasculitis.</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Asthma (including dyspnoea).</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Pneumonitis.</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia. Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation).</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis. Ischaemic colitis.</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Transaminases increased.</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Hepatitis, jaundice, liver disorder.</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Fulminant hepatitis, hepatic necrosis, hepatic failure.</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Rash.</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Urticaria.</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
</tr>
</tbody>
</table>
Very rare

Impotence.

**General disorders and administration site conditions**

| Rare | Oedema. |

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 dose (150 mg daily) and in long term treatment (see sections 4.3 and 4.4).

**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 listed in Appendix V*.

### 4.9 Overdose

**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 a severe case of overdosage a specialised hospital unit should be contacted immediately. 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.

The absorption from the GI-tract should be prevented as soon as possible. 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

**ATC code: M01AB05**

Diclofenac is a non-steroidal anti-inflammatory drug belonging to the group of arylacetic acid derivatives. Diclofenac has anti-inflammatory, analgesic and antipyretic effects. Its effect (as the effect of all NSAIDs) is at least partly based on the inhibition of the enzyme cyclo-oxygenase catalysing the synthesis of prostaglandins from arachidonic acid. In Diclofenac T ratiopharm tablets the active ingredient is diclofenac potassium.

**Paediatric population**

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

After oral administration, diclofenac is rapidly and completely absorbed. The peak plasma concentration is reached on average 20-60 minutes after administration of a 50 mg film-coated tablet. Due to first pass effect in the liver, the absolute oral bioavailability is approximately 50%.

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

The total systemic clearance of diclofenac in plasma is $263 \pm 56 \text{ ml/min}$ (mean value ± SD). The terminal half-life in plasma is 1-2 hours. The biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation. About 60 % of the administered dose is excreted in the urine in form of metabolites. Less than 1 % is excreted as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in the faeces.

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

No relevant age-dependent differences in the drug 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 < 10 ml/min, the theoretical steady-state plasma levels of 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 reveal no special hazard for humans, beyond the information included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, lactose monohydrate, maize starch, carmelllose sodium, magnesium stearate, anhydrous colloidal silica, hypromellose, glycerol 85 %, talc, titanium dioxide (E171), red and yellow ferric oxide (E172).

6.2 Incompatibilities

Not applicable.
6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

10, 20, 20x1, 30, 50, 50x1, 100, 100x1 film-coated tablets in PVC/Al blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2016-10-06