SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diclofenac T ratiopharm 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg diclofenac potassium.

Excipient(s) with known effect
Each film-coated tablet contains 93.5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Red-brown, round, film-coated tablet, diameter 9.1 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and adolescents over 16 years
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.

Paediatric population
Symptomatic, short-term treatment (children and adolescents) of
- pain related to inflammatory infections of the ear, nose or throat, e.g. pharyngotonsillitis, otitis (ENT). In keeping with general therapeutic principles, the underlying disease should be treated with anti-infective basic therapy, as therapeutically appropriate. Fever alone without inflammatory component is not an indication.
- acute post-operative pain after minor surgery (POP).

Diclofenac T ratiopharm tablets are not indicated for children under 9 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
Children aged 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, see table below.

Body weight (corresponding age)	Single dose	Maximum daily dose
35-44 kg BW (9-11 year)	25 mg	3 x 25 mg
45-55 kg BW (12-16 year)	25 mg	3-4 x 25 mg

Diclofenac T ratiopharm tablets are not indicated for children under 9 years of age due to the amount of diclofenac in each tablet.

Elderly
The lowest effective dose should be used especially when treating weak and low weight elderly patients (see also section 4.4).

Renal impairment
Diclofenac is contraindicated in patients with severe renal impairment (see section 4.3).
No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made.
Caution is advised when administering diclofenac to patients with mild to moderate renal impairment (see section 4.4).

Hepatic impairment
Diclofenac is contraindicated in patients with severe hepatic impairment (see section 4.3).
No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made.
Caution is advised when administering diclofenac to patients with mild to moderate hepatic impairment (see section 4.4).

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.
- 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) (see sections 4.4 and 4.8).
- 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
- Conditions with increased bleeding propensity including bleeding diathesis.
- Hepatic porphyria.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients, in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs (so-called cross-reactions with NSAIDs) (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

General
Undesirable effects may be minimised by using the lowest effective dose for the shortest 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, i.e. coxibs, 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.
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. 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.

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 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 (see section 4.2).

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA/aspirin) or other medicinal products likely to increase gastrointestinal risk (see below and section 4.5).

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 any disease of the gastrointestinal tract, such as ulcerative colitis or Crohn’s disease, as their condition may be exacerbated (see section 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.

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, toxic epidermal necrolysis, and generalised bullous fixed drug eruption have been reported very rarely in association with the use of diclofenac (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 congestive heart failure (NYHA class I) 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 congestive heart failure (NYHA I) and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.
Diclofenac should not be used in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see section 4.3).
As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Patients should remain alert for the signs and symptoms of serious, acute arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

Haematological effects
Use of 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.

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.

General information

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

Excipient(s)

Lactose
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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.

CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with 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.

CYP2C9 inducers: Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin, carbamazepine and barbiturates), which could result in a significant decrease in plasma concentration and exposure to 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.

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, ACE inhibitors or *Angiotensin II antagonists* due to the increased risk of nephrotoxicity (see section 4.4).

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

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 (such as warfarin) 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. Isolated cases of metabolic acidosis have been reported in patients receiving diclofenac concomitantly with metformin, particularly if they have a history of renal impairment.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %.
The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.
In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

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 (see section 4.3 and 5.3).

Breast-feeding
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 (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 (see section 4.8) while taking diclofenac, should refrain from driving or using machines.

4.8 Undesirable effects

The adverse reactions presented in Table 1, reported in clinical trial and/or post-marketing reports or in literature, are grouped by MedDRA system organ class.

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).

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

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).

Gastrointestinal
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 and colitis or exacerbation of Crohn's disease (see section 4.4) have been reported following administration. Gastritis has been reported in rare cases.

Table 1
The following undesirable effects include those reported with either short-term or long-term use of diclofenac gastro-resistant tablets and/or other diclofenac formulations.

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). Angioedema (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 impairment, vision blurred, diplopia.
Ear and labyrinth disorders	
Common Very rare	Vertigo. Tinnitus, hearing impaired.
Cardiac disorders	
Uncommon* Not known	Palpitations, chest pain, cardiac failure, myocardial infarction. Kounis syndrome
Vascular disorders	
Very rare	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare Very rare	Asthma (including dyspnoea). Pneumonitis.
Gastrointestinal disorders	
Common Rare Very rare	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia. Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding, gastrointestinal obstruction or perforation that may lead to peritonitis). Colitis (including haemorrhagic colitis, ischaemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder,

	diaphragm-like intestinal strictures, pancreatitis.
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 Not known	Rash. Urticaria. Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura , allergic purpura (Henoch-Schonlein), pruritus. Fixed drug eruption Generalised bullous fixed drug eruption.
Renal and urinary disorders	
Very rare	Acute kidney injury (acute renal failure), haematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare	Oedema.

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

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.

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 and antirheumatic products, non-steroids, acetic acid derivatives and related substances (NSAID) (ATC code: M01A B05).

Mechanism of action
Diclofenac T ratiopharm tablet contains the potassium salt of diclofenac, a non-steroidal compound with anti-inflammatory, analgesic, and antipyretic properties.

Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing of inflammation, pain, and fever.

Pharmacodynamic effect
In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterised by relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

In post-traumatic and post-operative inflammatory conditions, diclofenac relieves both pain at rest and pain on movement and reduces inflammation and swelling.

Clinical studies have also revealed that, in primary dysmenorrhoea, diclofenac is capable of relieving the pain and reducing the extent of bleeding.

Diclofenac inhibits renal prostaglandin synthesis. In patients with normal renal function, this effect is not significant. In patients with chronic renal, cardiac or hepatic insufficiency and conditions with plasma volume changes, the inhibition of prostaglandin synthesis may lead to acute renal failure, fluid retention and heart failure (see section 4.3).

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

Absorption
Diclofenac is rapidly and completely absorbed.

The maximum concentration in plasma is reached approximately 20-60 minutes after ingestion of a 50 mg tablet. The quantity of active substance that is absorbed is not reduced when the tablet is ingested together with food.

Since about half of the active substance undergoes first-pass metabolism in the liver, the AUC after oral administration will remain at only about half the AUC after an equal parenteral dose.

The pharmacokinetic properties are unchanged following repeated administration. No accumulation occurs in the recommended dosage interval.

Distribution
Diclofenac binds almost completely (99.7%) to proteins in plasma, mainly to albumin (99.4%). The calculated volume of distribution is 0.12 - 0.17 l/kg.

Diclofenac is distributed to the synovial fluid, in which the maximum concentration is reached after 2-4 hours after reaching the maximum plasma concentration. The half-life of the elimination phase in synovial fluid is 3-6 hours. By two hours after reaching the maximum plasma concentration, the concentration of active substance is already higher in the synovial fluid than in plasma and remains so for 12 hours.

Metabolism
Diclofenac is partially metabolised by direct glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation reactions, resulting in several different phenolic metabolites (3-hydroxy, 4-hydroxy, 5-hydroxy, 4,5-hydroxy and 3-hydroxy-4-methoxyclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination
The total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean ± SD). The half-life of the terminal phase in plasma is 1-2 hours. The plasma half-lives of four metabolites (including two active metabolites) are also short; 1-3 hours. The half-life of one specific metabolite, 3-hydroxy-4-methoxyclofenac, is significantly longer. However, this metabolite is virtually inactive.

About 60% of the administered dose is excreted in the urine as the glucuronide metabolite of diclofenac and as other metabolites, most of which are also in the glucuronide form. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites via bile in the faeces.

Linearity/non-linearity
The amount of drug absorbed is directly related to the dose administered.

Specific patient groups
No relevant age-dependent differences in the drug absorption, metabolism or excretion have been observed.

In patients with renal insufficiency, accumulation of the unchanged active substance cannot be demonstrated based on single-dose kinetics when using the usual dose interval. At a creatinine clearance of < 10 mL/min, the theoretical steady-state plasma concentrations of the hydroxy metabolites are approximately four times higher than in healthy subjects. Metabolites are finally eliminated through the bile.

In patients with chronic hepatitis or uncompensated 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 SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

10, 20, 30, 30x1, 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

2025-08-27
{DD month YYYY}
[To be completed nationally]