SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diclo-Denk 100 Retard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: diclofenac sodium

Each prolonged-release tablet contains 100 mg diclofenac sodium.

Excipient with known effect: Each prolonged-release tablet contains 119.0 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Round, brown-red biconvex tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of pain and inflammation in case of:
- acute arthritides (including gout attack)
- chronic arthritides, especially rheumatoid arthritis (chronic polyarthritis)
- ankylosing spondylitis (Bechterew's disease) and other inflammatory rheumatoid disorders of the spine
- acute inflammatory condition of arthroses and spondylarthroses
- inflammatory soft tissue rheumatisms
- painful swelling or inflammation after injuries.

Due to the delayed release of active ingredient from Diclo-Denk 100 Retard, this preparation is not suitable for initiating therapy in patients where a rapid onset of effect is required.

4.2 Posology and method of administration

Posology
The dose of diclofenac depends on the severity of the illness. The recommended daily dose for adults is between 50 mg and 150 mg of diclofenac sodium.

Age	**Single dose**	**Total daily dose**
Adults	1 prolonged-release tablet (equivalent to 100 mg diclofenac sodium)	1 prolonged-release tablet (equivalent to 100 mg diclofenac sodium)

Method of administration
Diclo-Denk 100 Retard is swallowed whole with ample fluids. Patients with sensitive stomachs are advised to take Diclo-Denk 100 Retard with meals. Do not break the tablets.

The attending doctor will decide how long the treatment should take.

Prolonged intake of Diclo-Denk 100 Retard can be necessary for rheumatic diseases.

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

Special patient groups

Elderly patients
No particular dosage adjustment is required. Due to potential adverse drug reactions, elderly patients should be carefully monitored.

Impaired renal function
A dose reduction is not necessary in patients with slight to moderate renal impairment (patients with severe renal failure, see section 4.3).

Impaired liver function
A dose reduction is not necessary in patients with slight to moderate liver impairment. (Patients with severe liver impairment, see section 4.3).

Children and adolescents
Use of Diclo-Denk 100 Retard is not recommended in children or adolescents under 18 years of age, as the active ingredient content is too high.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Previous history of bronchospasm, asthma, rhinitis or urticaria after taking acetylsalicylic acid or other non-steroidal antirheumatics/antiphlogistics (NSAIDs)
- Unclarified impairment of blood cell formation
- Active or previous history of recurrent peptic ulcers or haemorrhage (2 or more episodes of proven ulceration or bleeding)
- History of gastrointestinal bleeding or perforation related to previous treatment with NSAIDs
- Cerebrovascular or other active bleeding
- Severe liver impairment (see section 4.4)
- Severe renal impairment (see section 4.4)
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease
- The last trimester of pregnancy (see section 4.6)

Diclo-Denk 100 Retard is not suitable for children or adolescents under 18 years of age.

4.4 Special warnings and precautions for use

Gastrointestinal effects
Concurrent treatment with diclofenac and other NSAIDs, including selective cyclooxygenase-2 inhibitors, should be avoided.

Adverse drug reactions may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and gastrointestinal and cardiovascular effects below).

Elderly patients
The elderly are at increased risk of adverse drug reactions in response to NSAIDs, including diclofenac, particularly gastrointestinal bleeding and perforation which may be fatal (see section 4.2). It is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Gastrointestinal bleeding, ulceration and perforation
Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs, including diclofenac. They occurred at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3) as well as in the elderly. These patients should commence treatment on the lowest dose available.

For these patients as well as those requiring concomitant therapy with low-dose acetylsalicylic acid or other medications that could increase the risk of gastrointestinal disorders (see section 4.5), combination therapy with a protective drug (such as misoprostol or a proton pump inhibitor) should be considered (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report all unusual abdominal symptoms, especially gastrointestinal bleeding, particularly in the initial stages of treatment.

Caution is advised in patients receiving concomitant treatment with medications which could increase the risk of ulceration or bleeding, such as oral and systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or platelet aggregation inhibitors such as acetylsalicylic acid (see section 4.5).

If patients develop any gastrointestinal bleeding or ulceration while taking diclofenac, the treatment should be discontinued.

Caution should be exercised when giving NSAIDs, including diclofenac, to patients with a history of gastrointestinal disease, such as ulcerative colitis or Crohn's disease, as these conditions may be exacerbated (see section 4.8).

Cardiovascular effects
Adequate medical surveillance and guidance of patients with a history of hypertension and/or slight heart failure (NYHA I) is necessary, as there have been reports of fluid retention and oedema related to NSAID treatment, including diclofenac.

Clinical studies and epidemiological data consistently point towards 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 section 4.3).

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
Patients should be alerted to signs and symptoms of severe arterial thrombotic events (e.g. chest pain, shortness of breath, weakness or speech disorders). These may occur without warning symptoms. Patients should be advised to contact a doctor immediately in such cases.

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome) have been reported in very rare cases in association with the use of NSAIDs, including diclofenac (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy, as these reactions occurred during the first month of treatment in the majority of cases. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

Hepatic effects
Close medical surveillance is required when prescribing diclofenac to patients with impairment of 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, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), diclofenac should be discontinued. Hepatitis may occur with 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 NSAIDs 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 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 therapy is usually followed by recovery to the pre-treatment state.

Haematological effects
During prolonged treatment with NSAIDs, including diclofenac, monitoring of the blood count is recommended. Diclofenac as well as other NSAIDs may reversibly inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

Other information
Diclofenac should only be used after careful consideration of the potential benefits and risks
- in case of congenital porphyrinopathy (e.g. acute intermittent porphyria)
- in case of systemic lupus erythematosus (SLE) as well as mixed connective tissue disease (see section 4.8).

Close medical surveillance is required in the following cases:
- impaired renal function
- impaired liver function
- immediately after major surgery (caution: increased tendency to bleeding or a worsening of kidney function)
- in patients who have had allergic reactions to other substances, as they are also at increased risk of developing hypersensitivity reactions when taking diclofenac.

Respiratory disorders
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.

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) have been observed in very rare cases when using diclofenac. This may also occur without previous exposure to this medicine. Treatment must be discontinued at the first sign of a hypersensitivity reaction after administration of diclofenac. The required symptomatic medical treatment must be carried out by a health care professional.

As with other NSAIDs, diclofenac, due to its pharmacodynamic properties, may mask the signs and symptoms of an infection.
If signs of an infection occur or worsen during treatment with diclofenac, the patient is advised to consult a doctor without delay. It should be checked whether anti-infective or antibiotic therapy is indicated.

Regular monitoring of renal function is required during long-term treatment with diclofenac.

Prolonged use of painkillers may cause headaches which must not be treated with higher doses of the medicinal product.

In general, habitual intake of painkillers, especially when several types of painkillers are combined, can result in permanent kidney damage with the risk of renal failure (analgesic nephropathy).

Concurrent use of NSAIDs, including diclofenac, with alcohol may enhance the adverse drug reactions, particularly those that affect the gastrointestinal tract or central nervous system.

Please refer to section 4.6 with regard to female fertility.

This medicine contains sucrose.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Other NSAIDs including salicylates
Concurrent use of several NSAIDs may increase the risk of gastrointestinal ulceration and haemorrhage due to a synergistic effect. Co-administration of diclofenac and other NSAIDs is therefore not recommended (see Section 4.4).

Digoxin, phenytoin, lithium
Concomitant administration of diclofenac and digoxin, phenytoin or lithium can increase plasma concentrations of these drugs. Monitoring of lithium levels in the blood is necessary. Monitoring of digoxin and phenytoin levels in the blood is recommended.

Diuretics, ACE inhibitors and angiotensin-II antagonists
NSAIDs may diminish the effect of diuretics and antihypertensives. In patients with impaired renal function (such as exsiccated patients or elderly patients with impaired renal function) concurrent use of an ACE inhibitor or angiotensin-II antagonist with a drug that inhibits cyclooxygenase may cause further deterioration of renal function including possible acute renal failure, which is reversible as a rule. Therefore, the combination should be used with caution and patients, particularly elderly, should have their blood pressure periodically monitored. Patients must be instructed to take sufficient fluids and regular monitoring of renal function should be considered after commencing combination therapy.

Drugs known to cause hyperkalemia
Concurrent treatment of diclofenac with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may cause hyperkalaemia. Therefore, monitoring of potassium levels in the blood is recommended frequently (see section 4.4).

Glucocorticoids

There is an increased risk of gastrointestinal reactions such as gastrointestinal ulceration or haemorrhage (see section 4.4).

Methotrexate
If diclofenac is taken within 24 hours before or after the administration of methotrexate, the concentration of methotrexate in the blood and its toxic effect may increase.

Ciclosporin
NSAIDs (such as diclofenac sodium) may increase the renal toxicity of ciclosporin.

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

NSAIDs may enhance the effect of anticoagulants such as warfarin (see section 4.4).

Increased risk of gastrointestinal bleeding and gastrointestinal side effects (see section 4.4).

Antidiabetics
There have been isolated reports of influencing blood glucose levels (e.g. hypoglycaemia and hyperglycaemia) 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.

Probenecid
Medicines containing probenecid may delay the excretion of diclofenac.

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

Quinolone antibacterials
Cerebral convulsions may occur in isolated cases due to an interaction between quinolones and NSAIDs.

4.6 Fertility, pregnancy and lactation

Pregnancy
The inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo and foetal development. Data from epidemiological studies indicate an increased risk of miscarriage as well as cardiac defects and gastroschisis with the use of prostaglandin synthesis inhibitors, including diclofenac, in early pregnancy. It is assumed that the risk is higher with increasing doses and longer duration of therapy.

Animal studies have proven that the use of prostaglandin synthesis inhibitors, including diclofenac, causes an increase in pre-and post-implantation loss and embryo and foetal lethality. Further, there have been increased incidences of various malformations including cardiovascular deformities in animals that received a prostaglandin synthesis inhibitor, including diclofenac, during the phase of organogenesis.

Diclofenac should therefore only be given during the first and second trimester of pregnancy if absolutely necessary. If diclofenac is being used by a woman who is attempting to conceive or during the first or

second trimester of pregnancy, the dosage should be kept as low as possible and the duration of treatment as short as possible.

During the last trimester of pregnancy all prostaglandin synthesis inhibitors, including diclofenac, may:
- expose the foetus to the following risks:
  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
  - renal impairment that may progress to renal failure associated with oligohydramnios;
- expose mother and child to the following risks at the end of the pregnancy:
  - potential prolongation of bleeding time, inhibiting effect on platelet aggregation, that may occur even at very low doses;
  - inhibition of uterine contractions resulting in delayed onset and prolonged duration of labour.

Therefore, Diclofenac is contraindicated during the last trimester of pregnancy.

Breast-feeding
The active ingredient diclofenac and its metabolites pass in small quantities into breast milk. Since no adverse effects on infants have been made known to date, short-term use of the medicinal product should in general not require discontinuance of breast-feeding. However, if high doses are prescribed or if the medicine is to be taken over a long period of time to treat rheumatic illnesses, early weaning should be considered.

Fertility
The use of diclofenac, like the use of other drugs that are known to inhibit cyclooxygenase/prostaglandin synthesis, may cause impairment of female fertility and is therefore not recommended in women who are attempting to conceive. Withdrawal of diclofenac should be considered in women who are having difficulties becoming pregnant or who are undergoing investigation of infertility.

4.7 Effects on ability to drive and use machines

Since the use of diclofenac, especially at higher doses, can result in central nervous side effects such as tiredness, visual disturbances and dizziness, the ability to react, to drive a vehicle or to operate machines may be impaired in individual cases. This applies in particular in combination with alcohol.

4.8 Undesirable effects

Adverse drug reactions are classified as follows:
very common (≥1/10)
common (≥1/100 to <1/10)
uncommon (≥1/1,000 to <1/100)
rare (≥1/10,000 to <1/1,000)
very rare (<1/10,000)
not known (cannot be estimated on the basis of the available data).

The following undesirable effects include those reported with Diclo-Denk 100 Retard and/or other dosage forms of diclofenac during short-term and long-term use.

Please note that the following adverse drug reactions are mostly dose-dependent and may differ from individual to individual.

The most common adverse drug reactions affect the digestive tract. Peptic ulcers, perforation or bleeding, sometimes fatal, may occur, particularly in elderly patients (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, indigestion, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of ulcerative colitis and Crohn’s disease (see section 4.4) have been reported after use. Gastritis is less common.

Oedema, high blood pressure and heart failure have been reported in response to NSAID treatment, including diclofenac.

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).

Heart disease
Uncommon*: cardiac infarction, heart failure, palpitations, chest pain
Very rare: oedema

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

Blood and lymphatic system disorders
Very rare: impaired haematopoiesis (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis) haemolytic anaemia, aplastic anaemia

Initial symptoms could be: fever, sore throat, superficial lesions in the mouth, influenza-like complaints, severe lassitude, nose bleeding and dermatorrhagia.

The blood count should be monitored regularly during long-term therapy.

Nervous system disorders
Common: central nervous symptoms such as headache, vertigo, light-headedness, state of excitement, irritability or fatigue
Very rare: sensory disturbances, distortion of taste, impaired memory, disorientation, seizures, tremor, stroke

Eye disorders
Very rare: impaired vision (blurred and double vision)

Disorders of the ear and labyrinth
Common: vertigo
Very rare: tinnitus, temporary impaired hearing

Gastrointestinal disorders
Very common: gastrointestinal complaints such as nausea, vomiting and diarrhoea as well as minor gastrointestinal bleeding, which may cause anaemia in individual cases
Common: dyspepsia, flatulence, abdominal pain, abdominal cramps, loss of appetite as well as gastric or intestinal ulcers (sometimes with bleeding and perforation)
Uncommon: hematemesis, melaena or bloody diarrhoea
Rare: gastritis
Very rare: stomatitis (including ulcerative stomatitis), glossitis, lesions of the oesophagus, lower abdominal complaints (e.g. colitis, haemorrhaging inflammation of the colon or exacerbation of ulcerative colitis or Crohn's disease), constipation, pancreatitis, diaphragm-like intestinal strictures
Unknown: ischaemic colitis

The patient should be instructed to stop taking the medication if he experiences severe upper abdominal pain, melena or haematemesis and to seek medical help immediately.

Renal and urinary disorders
Uncommon: development of oedema especially in patients with arterial hypertension or renal failure
Very rare: renal tissue damage (interstitial nephritis, papillary necrosis) that may be associated with acute renal failure, proteinuria and/or haematuria; nephrotic syndrome, acute renal failure

Renal function should therefore be monitored regularly.

Skin and subcutaneous tissue disorders
Common: rash
Uncommon: alopecia
Very rare: exanthema, eczema, erythema, photosensitisation, purpura (including allergic purpura) and bullous skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome), dermatitis exfoliative, erythrodermia

Infections and parasitic diseases
There have been very rare reports of exacerbation of infective inflammations (e.g. development of necrotic fasciitis) in association with systemic use of NSAIDs. This could be related to the mechanism of action of NSAIDs.

If signs of an infection occur or worsen during treatment with diclofenac, the patient is advised to consult a doctor without delay. It should be checked whether anti-infective or antibiotic therapy is indicated.

In very rare cases, the use of diclofenac has been associated with symptoms of aseptic meningitis such as stiff neck, headache, nausea, vomiting, fever or clouding of consciousness. Patients with autoimmune diseases, such as SLE or mixed connective tissue disease, seem to be predisposed to this.

Vascular disorders
Very rare: hypertension, vasculitis

Immune system disorders
Common: hypersensitivity reactions such as skin rash and itching
Uncommon: urticaria

In such a case, the patient is advised to contact a doctor immediately and to stop taking diclofenac.

Rare: anaphylactic and anaphylactoid reactions (including hypotension and shock)
Very rare: Severe general hypersensitivity reactions such as angioedema (including facial oedema), swelling of the tongue, inner swelling of the larynx with restriction of the respiratory passages, laboured breathing, palpitations, fall in blood pressure and eventually life-threatening shock.

If any of these symptoms occur, and this is possible following the first administration, immediate medical attention is required, and diclofenac should be discontinued.

Very rare: allergic vasculitis and pneumonitis

Hepatobiliary disorders
Common: rise in serum transaminases
Uncommon: liver damage, especially during long-term therapy, acute hepatitis with or without icterus (in very rare cases taking a fulminant course, sometimes without prodromal symptoms)
Very rare: hepatic necrosis, hepatic failure

Regular monitoring of liver parameters is therefore necessary during long-term therapy.

Psychiatric disorders:
Very rare: Psychotic reactions, depression, feelings of anxiety, nightmares, insomnia

Respiratory, thoracic and mediastinal disorders
Rare: asthma (including dyspnoea)
Very rare: pneumonitis

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.

4.9 Overdose

Symptoms of an overdose
Symptoms of an overdose may be central nervous symptoms such as headache, dizziness, light-headedness, tinnitus, convulsions, hyperventilation, disturbed consciousness and loss of consciousness (myoclonic seizures may occur in children) as well as abdominal pain, nausea, vomiting and diarrhoea. Gastrointestinal bleeding and liver and renal impairment may also occur. Hypotension, respiratory depression and cyanosis are further symptoms. In the case of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measures in case of overdose
Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment.
A specific antidote does not exist. 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 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 antiphlogistic and antirheumatic agent; acetic acid derivative and related substances

ATC Code: M01AB05

Diclofenac is a non-steroidal antiphlogistic/antirheumatic agent which proved to be effective in standard animal experiments on inflammation by inhibiting prostaglandin synthesis. In humans diclofenac reduces inflammatory pain, swelling and fever. Diclofenac also inhibits ADP and collagen-induced platelet aggregation.

5.2 Pharmacokinetic properties

After oral application of the standard enteric coated pharmaceutical form, diclofenac is completely absorbed distally from the stomach. Maximum plasma levels are reached within 1 - 16 hours depending on how long passage through the stomach takes and are reached on average within 2 – 3 hours. Maximum plasma levels are reached within 10 – 20 minutes after IM administration and approx. 30 minutes after rectal administration. Orally administered diclofenac is clearly subject to a first pass effect; only 35 – 70 % of the absorbed active ingredient reaches post-hepatic circulation in unchanged form. Approx. 30 % of the active ingredient is metabolised and excreted in the faeces.

Approximately 70 % is eliminated renally after hepatic metabolisation (hydroxylisation and conjugation) in the form of pharmacologically inactive metabolites. Largely independent of hepatic and renal function, the elimination half-life is approximately 2 hours. The plasma protein binding is approx. 99 %.

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

5.3 Preclinical safety data

Based on conventional studies on safety pharmacology, genotoxicity and carcinogenic potential, preclinical data have revealed no special hazard for humans beyond those addressed in other sections. In animal studies chronic toxicity of diclofenac was characterised predominately as gastrointestinal lesions and ulcers. In a two-year toxicity study a dose-dependent increase in thrombotic vascular occlusion of the heart was observed in rats treated with diclofenac.

In studies on reproductive toxicity in animals diclofenac was observed to inhibit ovulation in the rabbit and interfere with implantation and early embryonal development in the rat. The duration of pregnancy and labour were prolonged by diclofenac. The embryotoxic potential of diclofenac was investigated in three animal species (rat, mouse, rabbit). Foetal death and growth retardation occurred at doses in the maternal-toxic range. Based on the available data, diclofenac is considered non-teratogenic. Doses below the maternal-toxic limit had no effect on the postnatal development of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Cetyl alcohol
Povidone
Colloidal anhydrous silica
Magnesium stearate
Hypromellose
Polysorbate 80
Macrogol 6000
Talc
Titanium dioxide
Ferric oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place below 25 °C. Protect from light.

6.5 Nature and contents of container

PVC/PVDC/aluminium blisters
Pack sizes: 10 or 100 prolonged-release tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBER IN GERMANY

5808.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

07.03.1985

10. DATE OF REVISION OF THE TEXT

09/2017

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription