SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Olfen™-75 SR, prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance
Diclofenac sodium

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Prolonged-release tablets containing 75 mg

Description: Pink, round, biconvex film-coated tablets embossed “75” on one side and “SR” on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, including spondyloarthritis.

Painful spinal syndromes.

Extra-articular rheumatism.

Painful conditions of inflammation and swelling following trauma and surgical procedures, e.g. in dental and maxillofacial surgery and in orthopaedics.

Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhea, adnexitis. As an adjuvant in acute painful inflammatory infections of the ears, nose or throat, e.g. pharyngotonsillitis.

In accordance with general medical principles, appropriate therapeutic measures should be taken for the treatment of underlying diseases. Fever alone is not an indication.

4.2 Posology and method of administration
Generally, it is advisable to select the dose on an individualised basis. Adverse reactions can be reduced by administering the lowest effective dose over the shortest possible duration for symptomatic control (see “Warnings and precautions”).

Adults
In general, the daily dose of Olfen™ SR is 100-150 mg, i.e. two 75 mg prolonged-release tablets or one 100 mg prolonged-release capsule, which is available under the commercial name of Olfen™-100 SR. For relatively mild cases and long-term treatment, one 75 mg prolonged-release tablet or one 100 mg prolonged-release capsule per day is generally sufficient. If the symptoms occur most severely during the night or in the morning, prolonged-release Olfen™ should preferably be taken in the evening. The prolonged-release tablets should be taken unchewed with some liquid, preferably with meals.

Special dosage instructions
Paediatric population
Due to their active substance content, Olfen™-75 SR containing 75 mg are not suitable for children and adolescents.

Depending on the severity of the disease, children aged 1 year and older and adolescents should be given 0.5-2 mg per kg body weight daily, divided into 2-3 single doses. For the treatment of juvenile rheumatoid arthritis, the daily dose can be increased to a maximum of 3 mg per kg body weight, divided into several single doses.
The maximum daily dose of 150 mg should not be exceeded.

Olfen™ must not be used in children under 1 year of age.

Olfen™ tablets containing 25 mg, available under the commercial name of Olfen™ 25/50 gastro-resistant tablets, can be used in these patients.

Elderly patients (65 years and older)
Generally speaking, no initial dose adjustment is necessary in elderly patients. However, caution should be exercised in elderly patients for fundamental medical reasons; especially in frail elderly patients or those with a low body weight (see “Warnings and precautions”).

Existing cardiovascular disease or significant cardiovascular risk factors
Treatment with Olfen™ is generally not recommended in patients with existing cardiovascular disease or uncontrolled hypertension. If necessary, patients with existing cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease should not be treated with Olfen™ until after a careful assessment and if administered for more than 4 weeks they should not receive doses exceeding 100 mg per day (see “Warnings and precautions”).

Patients with renal insufficiency
Olfen™ is contraindicated in patients with renal insufficiency (GFR <15 mL/min/1.73 m^2) (see
“Contraindications”).

No specific studies have been conducted in patients with impaired renal function and it is therefore not possible to make specific dose adjustment recommendations. Caution is required when administering Olfen™ to patients with renal function impairment (see “Warnings and precautions”).

Patients with hepatic impairment
Olfen™ is contraindicated in patients with hepatic insufficiency (see “Contraindications”).
No specific studies have been conducted in patients with impaired hepatic function and it is therefore not possible to make specific dose adjustment recommendations. Caution is required when administering Olfen™ to patients with mild to moderate hepatic function impairment (see “Warnings and precautions”).

4.3. Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in the composition.
History of bronchospasm, urticaria, acute rhinitis, nasal polyps or allergy-like symptoms after taking acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.

Third trimester of pregnancy (see “Pregnancy/Lactation”).
Active gastric and/or duodenal ulceration, or gastrointestinal haemorrhage or perforation.
Inflammatory bowel diseases (such as Crohn's disease, ulcerative colitis).
Hepatic insufficiency (Child-Pugh class C) (hepatic cirrhosis and ascites).
Renal failure (GFR <15 mL/min/1.73 m^2).
Severe cardiac failure (NYHA III-IV).

Treatment of postoperative pain after coronary bypass surgery (or use of a heart-lung machine).

4.4. Special warnings and precautions for use
General warning about the use of systemic non-steroidal anti-inflammatory drugs
Gastrointestinal ulceration, bleeding or perforation may occur at any time during treatment with non-steroidal anti-inflammatory drugs (NSAIDs), whether COX-2 selective or not, even without warning symptoms or a relevant previous history. To minimise this risk, the lowest effective dose should be administered for the shortest possible duration.
Placebo-controlled studies have demonstrated that certain selective COX-2 inhibitors increase the risk of thrombotic cardiovascular and cerebrovascular complications. It is not yet known whether this risk correlates directly to the COX-1/COX-2 selectivity of the individual NSAIDs. Since no comparable clinical study data are currently available for

diclofenac at maximum dosage and during long-term therapy, the possibility of a similarly high risk cannot be ruled out. Until relevant data are available, diclofenac should be used in clinically confirmed cases of coronary heart disease, cerebrovascular disease, peripheral arterial occlusive disease, or in patients with significant risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) only after careful consideration of the benefits and risks. Also because of this risk, the lowest effective dose should be administered for the shortest possible duration.

The renal effects of NSAIDs entail fluid retention with oedema and/or arterial hypertension. Diclofenac should therefore be used only with caution in patients with impaired cardiac function and other conditions that predispose them to fluid retention. Caution is also advised in patients taking diuretics or ACE inhibitors concomitantly, as well as in those with an increased risk of hypovolaemia.

In the elderly, the consequences are generally more serious. If gastrointestinal bleeding or ulceration occurs in patients on Olfen™ treatment, administration of the medicinal product should be discontinued.

Skin reactions
Serious, sometimes fatal, skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have very rarely been associated with the use of NSAIDs, including diclofenac (see “Undesirable effects”). The risk to the patients appears to be greatest at the start of treatment, and the reaction mostly subsides within the first month of treatment. Olfen™ should be discontinued at the first sign of skin rash, mucosal lesions or other signs of hypersensitivity.

As with other NSAIDs, diclofenac can in rare cases result in allergic reactions, including anaphylactic/anaphylactoid reactions, even without prior exposure to the medicinal product.

Masked signs of infection
The pharmacodynamic properties of Olfen™ mean that – as with other NSAIDs – the signs and symptoms of an infection can be masked.

Precautions
General
The concomitant use of Olfen™ and systemic NSAIDs, such as selective cyclooxygenase-2 inhibitors, must be avoided since there is a potential for additive undesirable effects (see “Interactions”).

For fundamental medical reasons, caution is necessary in elderly patients. In frail elderly patients or those with a low body weight in particular, it is advisable to administer the lowest effective dose.

Olfen™-75 SR contain lactose. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Olfen™-75 SR.

Respiratory effects (pre-existing asthma)
Reactions to NSAIDs, such as exacerbated asthma (referred to as analgesic intolerance/ analgesic asthma), Quincke’s oedema or urticaria, are more common in patients with asthma, seasonal allergic rhinitis, nasal mucosa swelling (e.g. nasal polyps), chronic obstructive pulmonary disease or chronic respiratory tract infection (especially if associated with allergic rhinitis-like symptoms) than in other patients. Therefore, special caution should be exercised in these patients (readiness for an emergency). This also applies to patients who experience allergic reactions to other substances in the form of skin rash, pruritus or urticaria, for instance.
Gastrointestinal effect
As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution required when prescribing Olfen™ to patients with symptoms indicative of gastrointestinal (GI) disorders, or to patients with a history of gastric or intestinal ulceration,

bleeding or perforation (see “Undesirable effects”). The risk of GI bleeding is greater at higher NSAID doses as well as in patients with a history of ulceration, particularly if additionally complicated by bleeding or perforation, and in the elderly.

To reduce the risk of GI toxicity in patients with a history of ulceration, particularly if additionally complicated by bleeding or perforation, and in the elderly, 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 in these patients, and also in patients requiring concomitant low-dose acetylsalicylic acid (ASA) or other medicinal products likely to increase the gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, antiplatelet agents or selective serotonin reuptake inhibitors (see “Interactions”).

Hepatic effect
Close medical surveillance is necessary when prescribing Olfen™-75 SR to patients with impaired hepatic function, since their condition may be exacerbated (see “Undesirable effects”).

As with all NSAIDs, including diclofenac, the levels of one or more liver enzymes may increase during treatment with Olfen™-75 SR. This has been reported very commonly (in approx. 15% of patients) in clinical trials of diclofenac, but was rarely accompanied by clinical symptoms. In the majority of these cases, the increases were marginal. Commonly (in 2.5%), moderate increases were observed (≥3-<8 times the upper limit of normal) whereas the incidence of marked increases (≥8 times the upper limit of normal) remained at approximately 1%. In the aforementioned clinical trials, 0.5% of patients had clinically manifest liver damage in addition to elevated liver enzyme levels. The increases in the enzyme levels were generally reversible after discontinuation of the medicinal product. As with other NSAIDs, liver enzyme levels should also be monitored regularly during long-term Olfen™-75 SR therapy.

Olfen™-75 SR should be discontinued if liver function test results are abnormal or deteriorate, or if clinical signs or symptoms indicative of developing liver disease, or other manifestations (e.g. eosinophilia, skin rash) occur.

In addition to liver enzyme elevations, there have been rare cases of severe hepatic reactions, including jaundice and fulminant hepatitis, liver necrosis and hepatic failure, which were fatal in isolated cases.

Hepatitis can occur without prodromal symptoms. Olfen™-75 SR is to be used with caution in patients with hepatic porphyria, since it can induce an attack.

Renal effects
Given that prostaglandins play an important role in maintaining renal perfusion, oedema and hypertension commonly (1-10%) result from prolonged periods of treatment with high doses of NSAIDs, including diclofenac. Particular caution is required in patients with impaired cardiac or renal function; in patients with a history of hypertension; in elderly patients; in patients also taking diuretics or medications that have a considerable influence on renal function, as well as in patients with pronounced fluid deficiency in the extracellular space due to any cause, e.g. before or after a major surgical procedure (see “Contraindications”). Monitoring of renal function is recommended as a precautionary measure if Olfen™ is used in such cases. The patient usually returns to his/her pretreatment condition on discontinuation of treatment.

Cardiovascular effects
Treatment with NSAIDs, including diclofenac, can be associated with a slight, increased risk of severe cardiovascular thrombotic events (including myocardial infarction and stroke), especially at high doses and over prolonged periods.

Treatment with Olfen™ is generally not recommended in patients with existing cardiovascular disease (cardiac failure, existing ischaemic heart disease, peripheral arterial occlusive disease) or uncontrolled hypertension. If necessary, patients with existing cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should not be treated with Olfen™ until after a careful assessment and if treatment is continued for more than 4 weeks they should not receive doses exceeding 100 mg/day.

As the cardiovascular risk factors of diclofenac can increase with the dose and duration of administration, the lowest effective daily dose should be used for the shortest possible duration. The patient's need for symptomatic relief and the response to the treatment should be reviewed periodically, particularly if the treatment is continued for more than 4 weeks. The patient should be alert to signs and symptoms of serious arterial thromboembolic events (e.g. chest pain, shortness of breath, weakness, slurred speech), which can occur without warning. Patients should be instructed to consult a doctor immediately in the case of such events.

Haematological effects
Monitoring of the blood count is recommended during long-term treatment with Olfen™-75 SR, as with other NSAIDs.

Like other NSAIDs, Olfen™-75 SR can also temporarily inhibit platelet aggregation. Patients with a coagulation disorder should be closely monitored.

4.5 Interaction with other medicinal products and other forms of interaction
The following interactions have been observed with Olfen™-75 SR and/or other pharmaceutical forms of diclofenac.

Reported interactions to be considered
CYP2C9 inhibitors
Caution is recommended when administering diclofenac with CYP2C9 inhibitors (e.g. voriconazole). Significant increases in the peak plasma concentration of diclofenac and a general increase in overall exposure to diclofenac.

CYP2C9 inducers
Caution is recommended when administering diclofenac with CYP2C9 inducers (e.g. rifampicin). A significant reduction in the plasma concentration and exposure to diclofenac can occur.

Lithium
If co-administered, diclofenac can increase the plasma lithium concentration. Monitoring of serum lithium concentrations is recommended.

Digoxin
If used concomitantly, diclofenac can raise the plasma concentration of digoxin. Monitoring of serum digoxin concentrations is recommended.

Diuretics and antihypertensive agents
As with other NSAIDs, co-administration of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) can reduce their antihypertensive activity. Such a combination should therefore be administered with caution, and patients, the elderly in particular, should have their blood pressure monitored regularly. Patients should be adequately hydrated, and attention should be paid to monitoring renal function after initiating concomitant therapy as well as periodically thereafter, particularly

when using diuretics and ACE inhibitors due to the increased risk of nephrotoxicity (see “Warnings and precautions”).

Ciclosporin and tacrolimus
Diclofenac, like other NSAIDs, can increase the nephrotoxicity of ciclosporin and tacrolimus due to its effects on renal prostaglandins. Therefore, it should be given at doses lower than those given to patients not receiving ciclosporin or tacrolimus.

Medicinal products known to cause hyperkalaemia
Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim can be associated with elevated plasma potassium levels, which should therefore be checked frequently (see “Warnings and precautions”).

Quinolone antibiotics
There have been isolated reports of convulsions which were possibly attributable to the concomitant use of quinolones and NSAIDs.

Foreseeable interactions to be considered Other NSAIDs and corticosteroids
Co-administration of diclofenac with other systemic NSAIDs or corticosteroids can increase the frequency of adverse gastrointestinal reactions (See “Warnings and precautions”).

Anticoagulants and antiplatelet agents
Caution is recommended since concomitant administration could increase the risk of bleeding (see “Warnings and precautions”).

Although clinical trials do not appear to suggest that diclofenac influences the effect of anticoagulants, there have been reports of an increased risk of bleeding in patients receiving diclofenac and anticoagulants concomitantly. Such cases therefore need to be monitored closely.

Selective serotonin reuptake inhibitors (SSRIs)
Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs can increase the risk of gastrointestinal bleeding (see “Warnings and precautions”).

Antidiabetic agents
Clinical trials have demonstrated that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects following administration of diclofenac, requiring the dosage of the antidiabetic agents to be adjusted. For this reason, it is advisable to monitor the glycaemia level as a precautionary measure during combination therapy. There have also been isolated reports of metabolic acidosis when diclofenac was administered together with metformin, especially in patients with pre-existing impairment of renal function.

Methotrexate
Caution is advised when administering NSAIDs, including diclofenac, less than 24 hours before or after treatment with methotrexate, since the blood levels of methotrexate may rise and the toxicity of methotrexate may be increased.

Phenytoin
If phenytoin is used together with diclofenac, monitoring of the plasma phenytoin concentration is recommended, as an increase in phenytoin exposure can be expected.

4.6 Fertility, pregnancy and lactation
Fertility
Diclofenac can impair female fertility and thus is not recommended in women who wish to conceive. In women who are having difficulty conceiving or who are undergoing fertility tests, discontinuation of diclofenac should be considered.

In animals, impairment of male fertility cannot be ruled out based on the corresponding data (see “Preclinical data”). The relevance of these findings to humans is not clear.

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryofoetal development. Data from epidemiological studies suggest that the risk of miscarriage, as well as cardiac malformations and gastroschisis, is higher after use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with the dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been found to increase pre- and post-implantation loss and embryofoetal lethality. In addition, increased incidences of various malformations, including cardiovascular abnormalities, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic phase (see "Preclinical data").

Diclofenac should not be given during the first and second trimesters of pregnancy unless absolutely necessary. If diclofenac is used by a woman attempting to conceive, or during the first or second trimester of pregnancy, the dose and duration of treatment should be kept to a minimum.
Diclofenac is contraindicated during the third trimester of pregnancy. All prostaglandin synthesis inhibitors can:
- expose the foetus to the following risks:
  - Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension; see also "Preclinical data");
  - Impaired renal function, which may progress to renal failure with oligohydramnios;
- expose the mother and child to the following risks:
  - Possible prolongation of bleeding time, an inhibitory effect on platelet aggregation which may occur even at very low doses;
  - Inhibition of uterine contractions resulting in delayed or prolonged labour.

Lactation
As with other NSAIDs, small amounts of diclofenac are excreted in human milk. As a precaution, therefore, diclofenac should not be used in women who are breast-feeding. If treatment is essential, the baby should be switched to bottle feeding.

4.7. Effects on ability to drive and use machines
Patients who experience visual disturbances, dizziness, vertigo, somnolence or other central nervous system disorders while taking Olfen™-75 SR should refrain from driving or using machines.

4.8. Undesirable effects
The undesirable effects listed below include those reported with Olfen™-75 SR and/or other pharmaceutical forms of diclofenac used for short-term or long-term treatment.
Frequency data
"Very common" (≥1/10), "common" (<1/10, ≥1/100), "uncommon" (<1/100, ≥1/1,000), "rare" (<1/1,000, ≥1/10,000), "very rare" (<1/10,000).
Blood and lymphatic system disorders
Very rare: thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.

Immune system disorders
Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare: angioedema (including facial oedema).

Psychiatric disorders
Very rare: disorientation, depression, insomnia, nightmares, irritability, psychotic disorder.

Nervous system disorders
Common: headache, light-headedness.
Rare: somnolence.

Very rare: paraesthesia, memory disorders, convulsion, anxiety, tremor, aseptic meningitis, dysgeusia, cerebrovascular event.

Eye disorders
Very rare: visual disturbance, amblyopia, diplopia.
Ear and labyrinth disorders
Common: vertigo.
Very rare: tinnitus, impaired hearing.

Cardiac disorders
Uncommon*: myocardial infarction, cardiac failure, palpitations, chest pain.
Vascular disorders
Very rare: hypertension, vasculitis.

Respiratory disorders
Rare: asthma (including dyspnoea).
Very rare: pneumonitis.

Gastrointestinal disorders
Common: nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, bloating, decreased appetite.

Rare: gastritis, gastrointestinal bleeding, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis or perforation, which may lead to peritonitis).

Very rare: colitis (including haemorrhagic colitis, ischaemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, intestinal diaphragm disease, pancreatitis.
Olfen™-75 SR can produce chronic inflammatory states with pseudo-membranes and strictures in the lower intestinal tract (small and large intestine).

Hepatobiliary disorders
Common: transaminases increased.
Rare: hepatitis, jaundice, hepatic dysfunction.
Very rare: fulminant hepatitis, hepatic necrosis, hepatic failure.

Skin disorders
Common: skin rash.
Rare: urticaria.
Very rare: bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (acute toxic epidermolysis), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schönlein purpura, pruritus.

Renal and urinary disorders
Common: fluid retention, oedema, hypertension.
Very rare: acute renal damage (acute kidney failure), haematuria, proteinuria, tubulointerstitial nephritis, nephrotic syndrome, renal papillary necrosis.

General disorders
Rare: oedema.
* The frequency reflects data from long-term treatment with a high dose (150 mg/day).
Meta-analyses of controlled clinical trials and pharmaco-epidemiological data suggest that the use of diclofenac, particularly at high doses (150 mg daily) and over prolonged periods, can be associated with an increased risk of arterial thromboembolic events (e.g. myocardial infarction or stroke) (see "Warnings and precautions").

Effects on vision
Visual disturbances, such as visual deterioration, blurred vision and diplopia, seem to be a class effect of NSAIDs and are normally reversible after discontinuation of therapy. A

probable mechanism for visual disturbances is inhibition of the synthesis of prostaglandin and other similar substances, which can alter the regulation of retinal blood pressure and may lead to possible changes in vision. If such symptoms occur during treatment with diclofenac, an ophthalmological examination should be considered to exclude other causes.

4.9 Overdose
Symptoms
There is no typical clinical picture that results from diclofenac overdose. Overdose can cause symptoms such as vomiting, gastrointestinal bleeding, diarrhoea, dizziness, tinnitus or convulsions. Acute renal failure and liver damage can occur in the event of severe intoxication.

Therapeutic measures
Treatment for acute intoxication from NSAIDs, including diclofenac, essentially comprises supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be introduced in response to complications such as hypotension, renal failure, convulsions, gastrointestinal symptoms and respiratory depression.

Specific measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to their high protein-binding capacity and extensive metabolisation.

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

Mechanism of action/Pharmacodynamics
Olfen™ contains the sodium salt of diclofenac, a non-steroidal active substance with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties.

The inhibition of prostaglandin biosynthesis, demonstrated experimentally, is regarded as significant in terms of the mechanism of action. Prostaglandins play a considerable role in the development of inflammation, pain and fever. At concentrations equivalent to those reached in humans, Olfen™ does not suppress the *in vitro* biosynthesis of proteoglycans in cartilage.
Clinical efficacy
In the treatment of rheumatic diseases, the anti-inflammatory and analgesic properties bring about a marked improvement in symptoms such as pain at rest, pain on movement, morning stiffness, joint swelling, as well as an increase in functionality. In post-traumatic and postoperative inflammation, Olfen™ rapidly ameliorates spontaneous and movement-induced pain, and reduces inflammatory swelling and wound oedema.

In clinical trials, the pronounced analgesic activity was also observed in moderate and severe non-rheumatic pain. In primary dysmenorrhoea, it can relieve pain and also reduce the extent of bleeding.

5.2 Pharmacokinetic properties
Absorption
Judging by the amount of unchanged diclofenac and its hydroxylated metabolites recovered in the urine, the same amount of diclofenac is released and absorbed from Olfen™-75 SR as from Olfen™ gastro-resistant tablets. However, the mean systemic availability of diclofenac from Olfen™ SR is approximately 82% of that achieved with the same Olfen™ dose in the form of gastro-resistant tablets (possibly due to the release rate-dependent metabolism during the first pass through the liver). Due to the slower release of the active substance from Olfen™ SR, lower peak plasma concentrations are reached than after administration of gastro-resistant tablets.

Mean peak plasma concentrations of 0.4 µg/mL are achieved, on average, four hours after administration of a 75 mg prolonged-release tablet with modified release. Ingestion with a meal has no appreciable effect on the absorption and systemic availability of diclofenac.

On the other hand, mean plasma concentrations of 13 ng/mL are measured 16 h after ingestion of Olfen™-75 SR, 75 mg).

When Olfen™-75 SR, 75 mg is taken twice daily, trough plasma concentrations are about 25 ng/mL.

Distribution
99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution can be calculated and is 0.12-0.17 L/kg, accordingly. Diclofenac penetrates the synovial fluid. Peak synovial fluid concentrations are measured 2-4 hours after the peak plasma concentrations have been reached. The apparent elimination half-life in the synovial fluid is 3-6 h. Two hours after the peak plasma concentrations are reached, the active substance levels in the synovial fluid are already higher than in the plasma and remain so for up to 12 hours.

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

Metabolism
Biotransformation of diclofenac is partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation. This results in several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxydiclofenac), which are then extensively conjugated to glucuronic acid. Two of these phenolic metabolites are pharmacologically active, albeit significantly less so than diclofenac.

Elimination
Diclofenac is eliminated from the plasma with a systemic clearance of 263 ± 56 mL/min (mean ± SD). The terminal half-life is 1-2 h. Four of the metabolites, including the two active metabolites, also have a short half-life of 1-3 h. The virtually inactive metabolite 3'-hydroxy-4'methoxy-diclofenac has a much longer half-life.
Approximately 60% of the administered dose is eliminated via the kidneys in the form of metabolites and less than 1% as unchanged substance. The remainder of the dose is eliminated as metabolites with the bile in the faeces.

Linearity/Non-linearity
There is a linear relationship between the absorbed and administered amount.

Kinetics in special patient groups
Relevant differences in absorption, metabolism and excretion due to patient age have not been observed.

In patients with impaired renal function, no accumulation of unchanged active substance can be inferred from the kinetics of a single dose for the usual dosage regimen. When creatinine clearance is less than 10 mL/min, the theoretical steady-state plasma level of the metabolites is approximately four times higher than in healthy people. Nevertheless, the metabolites are ultimately eliminated via the bile.

In case of impaired hepatic function (chronic hepatitis, compensated hepatic cirrhosis), the kinetics and metabolism of diclofenac are the same as in patients with a healthy liver.

5.3 Preclinical safety data

Non-clinical data from studies of safety pharmacology, acute toxicity and repeated dose toxicity as well as from genotoxicity, mutagenicity and carcinogenicity studies with diclofenac reveal no special hazard for humans at the intended therapeutic dosages.

The increased incidence of lymphoma (thymus) in mice, and the increased incidence of subcutaneous fibromas, fibroadenomas (mammary gland) or C-cell adenomas (thyroid) in rats, were all within the historical control range of the laboratory for the tested animal strain and were classified as coincidental.

All the toxicity studies performed on rats reported hypertrophy of the mesenteric lymph nodes or lymphadenitis with reactive hyperplasia. These changes were accompanied by neutrophilia, which was also observed in the studies on monkeys. These reactions are suspected to be secondary to the ulcers noted in the gastrointestinal tract. In a 2-year study with diclofenac in rats, a dose-dependent increase in thrombotic vascular occlusions in the heart was reported.
Additional studies suggested that fertility was influenced (reduced testosterone levels and decreased epididymal and testicular weights combined with histopathological changes) in rats given repeated oral doses of diclofenac (> 1 mg/kg body weight). Similar effects were also observed in the F1 generation after doses of ≥1.25 mg/kg in a 2nd generation study. In dogs, a daily subcutaneous dose of 2 mg/kg diclofenac sodium resulted in an increased sperm count. Other studies report that the percentage of mating female rats was reduced following repeated diclofenac doses of ≥0.5 mg/kg. Hence, an influence on both male and female fertility cannot be ruled out.

Diclofenac crosses the placental barrier in rodents. The administration of NSAIDs (including diclofenac) inhibited ovulation in rabbits, implantation and placentation in rats, and premature closure of the ductus arteriosus in pregnant rats. In rats, maternal toxic doses of diclofenac were linked to dystocia, prolonged gestation, decreased foetal survival and delayed intrauterine growth. The minimal effects of diclofenac on reproduction parameters and birth, as well as on closure of the ductus arteriosus in utero, represent the pharmacological activity of this class of prostaglandin synthesis inhibitors (see “Contraindications” and “Pregnancy/Lactation”).

Teratogenicity (cleft palate) was noted at the maternal toxic dose of 4 mg/kg in a study of mice. No teratogenic effects were reported in rats and rabbits treated with doses up to the maternal toxic level. Delayed ossification and reduced foetal weight in one study of rabbits were the only changes observed in these tests.
At maternal toxic doses, perinatal and postnatal development of the progeny was adversely affected (for fertility see above, as well as birth weight and delayed postnatal growth).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, hypromellose, talc, magnesium stearate, titanium dioxide, iron oxide red, macrogols.

6.2 Incompatibilities

Not applicable.

6.3. Shelf life

60 months.
The product may only be used until the date marked with “EXP” on the pack.

6.4 Special precautions for storage

Store in the original package.
Do not store above 30°C. Keep out of the reach and sight of children.

6.5. Nature and contents of container

At pharmacies, on medical prescription only.

Olfen™-75 SR: pink, round, biconvex prolonged-release tablets embossed “75” on one side and “SR” on the other side, in packs (cardboard box containing PVC-PVDC/Aluminium blisters) of 20, 30 and 100 prolonged-release tablets.
Not all dosages and packs sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7. Marketing Authorization Holder and Manufacturing site addresses
Acino Pharma AG, Birsweg 2, 4253 Liesberg, Switzerland.

8. Marketing Authorization Number
TAN 22 HM 0101

9. Date of first registration
11/04/2022

10. Date of Revision of the Text