1. NAME OF THE MEDICINAL PRODUCT

Olfen-25/50 *Lactab*

Olfen-75 SR *Depotabs*

Olfen-100 SR *Depocaps*

Olfen-50/100 *Rectocaps*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Olfen-25 Lactab

Each tablet contains:
Diclofenac sodium: 25 mg

Olfen-50 Lactab

Each tablet contains:
Diclofenac sodium: 50 mg

Olfen-75 SR Depotabs

Each tablet contains:
Diclofenac sodium: 75 mg

Olfen-100 SR Depocaps

Each capsule contains:
Diclofenac sodium: 100 mg

Olfen-50 Rectocaps

Each rectal capsule contains:
Diclofenac sodium: 50 mg

Olfen-100 Rectocaps

Each rectal capsule contains:
Diclofenac sodium: 100 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Olfen-25 Lactab

Gastro-resistant tablets.

Ochre yellow, biconvex, film-coated tablets, embossed “mp” and “o 25”.

Olfen-50 Lactab

Gastro-resistant tablets.

Ochre yellow, biconvex film-coated tablets, embossed “mp” and ˝o 50˝.

Olfen-75 SR Depotabs

Prolonged-release tablets.

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

Olfen-100 SR Depocaps

Prolonged-release capsules, hard.

Hard gelatin capsules with a pink cap and a white opaque body imprinted “Olfen 100” and containing the active substance in prolonged-released pellets.

Olfen-50 Rectocaps

Rectal capsules

Ivory coloured soft gelatine rectal capsules.

Olfen-100 Rectocaps

Rectal capsules

Pink coloured soft gelatine rectal capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inflammatory and degenerative forms of rheumatism: chronic polyarthritis, juvenile chronic polyarthritis, ankylosing spondylitis, osteoarthritis, including spondylarthrosis, painful cervical syndrome.

Extra-articular rheumatic disorders.

Painful conditions of inflammation and swelling after trauma and surgery, e.g. in dentistry/orthodontics, and orthopaedics.

Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea, adnexitis.

Migraine attacks (*Olfen Rectocaps*).

Acute attack of gout *(Olfen Lactab, Olfen Rectocaps).*

As an adjuvant in acute, painful inflammatory throat, nose or ear infections, e.g. pharyngotonsillitis, otitis *(Olfen Lactab, Olfen Rectocaps)*.

In accordance with general medical principles, appropriate therapeutic measures must be taken for treating the underlying disease. Fever alone is not an indication.

4.2 Posology and method of administration

As a general recommendation, the dose should be individually adjusted and the lowest effective dose administered for the shortest possible duration. The tablets and capsules are to be taken before a meal without chewing, together with a glass of water.

Adults

Olfen-25/50 Lactab, Olfen-50/100 Rectocaps

The initial daily dose of Olfen-25/50 Lactab and Olfen-50/100 Rectocaps is usually 100 – 150 mg. For less severe cases and long-term therapy, 75 – 100 mg per day is sufficient in most cases.

In general, the daily dose is divided into 2 – 3 individual doses.

To prevent nocturnal pain and morning stiffness, administration of a rectal capsule before bedtime can be combined with tablets during the day (up to a maximum daily dose of 150 mg).

For primary dysmenorrhoea, the daily dose, individually adjusted, is generally 50 - 150 mg; an initial dose of 50 – 100 mg should be selected and, if required, increased over several menstrual cycles up to a maximum of 200 mg/day. Therapy should be initiated when initial symptoms occur and should continue for several days, depending on the symptoms.

The rectal capsules should be inserted deep into the rectum, preferably after a bowel movement.

Treatment of migraine attacks with Olfen rectal capsules should be initiated with a dose of 100 mg at the first signs of an impending attack. Additional rectal capsules at a dosage of up to 100 mg can be used on the same day, if necessary. If further treatment is required on the following day, the maximum daily dose should not exceed 150 mg, administered in divided doses.

Olfen-75 SR Depotabs, Olfen-100 SR Depocaps

The daily dose is generally 100 – 150 mg, i.e. 1 capsule of Olfen-100 SR Depocaps or 2 tablets of Olfen-75 SR Depotabs. For milder cases and long-term treatment, 1 tablet of Olfen-75 SR Depotabs or 1 capsule of Olfen-100 SR Depocaps per day is generally sufficient. If the symptoms are at their most severe level during the night or in the morning, Olfen-75 SR Depotabs/Olfen-100 SR Depocaps should preferably be taken in the evening.

The tablets and capsules are to be taken before a meal, without chewing together with a glass of water.

Children and adolescents

Depending on the severity of the disease, children from the age of 1 year and adolescents are given 0.5 - 2 mg per kg body weight per day, divided into 2 - 3 individual doses. For the treatment of juvenile chronic polyarthritis, the daily dose, divided into several individual doses, can be increased up to a maximum of 3 mg per kg body weight.

The maximum daily dose of 150 mg should not be exceeded.

Olfen should not be used in children below 1 year of age.

Due to the high content of active substance, Olfen-50 Lactab and Olfen 50/100 Rectocaps are not recommended for use in children. Olfen-25 Lactab can be used in these patients.

Olfen-75 SR Depotabs and Olfen-100 SR Depocaps are not suitable for children and adolescents, respectively.

Olfen-50 Rectocaps are not recommended for children and adolescents below 14 years of age due to the amount of active substance; Olfen-100 Rectocaps are not suitable for children and adolescents.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of the product (see section 2 and section 6.1).
- History of allergic diseases such as bronchospasm, acute rhinitis, nasal polyps, urticaria following intake of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- Third trimester of pregnancy (see section 4.6).
- Active gastric and/or duodenal ulcer, or gastrointestinal haemorrhage, or perforation.
- Bowel inflammation such as Crohn's disease or ulcerative colitis.
- Severe liver insufficiency (hepatic cirrhosis and ascites).
- Severe renal insufficiency (creatinine clearance < 30 ml/min).
- Severe cardiac insufficiency (NYHA III-IV).
- Treatment of postoperative pain after coronary by-pass surgery (or use of a heart-lung machine).

Olfen Rectocaps: Proctitis.

4.4 Special warnings and special precautions for use

General warning on 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 (NSAID), whether COX-2 selective or otherwise, with or without warning signs or previous history. To minimise this risk, the smallest effective dose should be administered over the shortest possible duration of treatment.

An increased risk of thrombotic cardiovascular and cerebrovascular complications has been demonstrated for certain selective COX-2 inhibitors in placebo-controlled studies. It is not yet known whether this risk correlates directly with the COX-1/COX-2 selectivity of the individual NSAID. As there are currently no comparable clinical studies at the maximum dosage and in long-term therapy for diclofenac, a similarly increased risk cannot be excluded. Until relevant data are available, diclofenac should

be used in clinically confirmed coronary heart disease, cerebrovascular disease, peripheral arterial occlusive disease or in patients with major risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) only after careful analysis of the risks and benefits. Again, because of this risk, the smallest effective dose should be administered over the shortest possible duration of treatment.

The renal effects of NSAIDs include fluid retention with oedema and/or hypertension. Therefore, diclofenac should be used with caution in patients with impaired cardiac function and other conditions that predispose to fluid retention. Caution should also be exercised in patients concomitantly taking diuretics or ACE inhibitors and in those at increased risk of hypovolaemia.

Warnings

The consequences are generally more serious in the elderly. If gastrointestinal bleeding or ulceration occurs in patients during treatment with Olfen, the medicinal product should be withdrawn.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at greatest risk early in the course of therapy, the onset of reactions usually occurring within the first month of treatment. Olfen should be discontinued at the first signs of skin rash, mucosal lesions or any other sign of hypersensitivity.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can occur in rare cases, even in the absence of any previous treatment with diclofenac.

Owing to its pharmacodynamic properties, Olfen - like other NSAIDs - may obscure symptoms of an infection.

Precautions

General

Concomitant use of Olfen with systemic NSAIDs such as cyclo-oxygenase-2-selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse effects.

As a basic medical principle, caution is indicated in elderly. In particular, it is recommended that the lowest effective dose should be used in frail elderly subjects or those with a low body weight.

Olfen-75 SR Depotabs and Olfen-100 SR Depocaps contain lactose. Patients with hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Olfen-75 SR Depotabs and Olfen-100 SR Depocaps.

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, chronic obstructive pulmonary disease or chronic respiratory tract infections (especially if associated with allergic rhinitis-like symptoms), reactions to NSAIDs such as asthma exacerbation (so-called analgesic intolerance/analgesic asthma), Quincke’s oedema or urticaria are more

frequent than in other patients. Therefore, particular caution is recommended in these patients (readiness for emergency). This is also applicable for patients who are allergic to other substances, e.g. with skin rash, pruritus or urticaria.

Gastrointestinal effects

As with all NSAIDs, close medical supervision is imperative and particular caution should be exercised when prescribing Olfen 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 is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.

To reduce the risk of GI toxicity in the elderly, as well as in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, 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, as well as for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products likely to increase the gastrointestinal risk.

Patients with a previous history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin re-uptake inhibitors (see section 4.5).

Hepatic effect

As with other NSAIDs, levels of one or more liver enzymes may increase during treatment with Olfen/Olfen SR. This has been observed very commonly in clinical studies with diclofenac (in about 15 % of patients), but it is rarely accompanied by clinical symptoms. In the majority of such cases, these increases are within borderline. Commonly (in 2.5 % of cases), moderate increases have been observed (≥ 3 -< $8 \times$ upper limit of normal), whereas the incidence of marked increases ($\geq 8 \times$ upper limit of normal) was approximately 1 %. In the above-mentioned clinical studies, 0.5 % of patients suffered clinically manifest liver damage in addition to elevated liver enzymes.

Upon discontinuation of medication, increased enzyme levels generally reverted to normal.

As with other NSAIDs, liver function should be monitored regularly during long-term therapy with Olfen/Olfen SR.

Treatment with Olfen/Olfen SR should be discontinued, if there is an abnormal or deteriorating liver function, if clinical signs and symptoms of liver disease or other manifestations (e.g. eosinophilia, skin eruptions) occur. In addition to elevations in liver enzymes, there have been rare reported cases of serious hepatic reactions including jaundice and, in isolated cases, fatal fulminant hepatitis. Hepatitis may occur without prodromal symptoms. In patients suffering from hepatic porphyria, Olfen/Olfen SR should be used with caution, as the product may precipitate an attack.

Renal effects

Due to the important function of prostaglandins in maintaining renal circulation, oedema and hypertension commonly (1 - 10%) occur during prolonged therapy with high-dose NSAIDs. Particular care must be taken in the case of patients with impaired cardiac or renal function; previous history of hypertension; elderly patients; patients taking diuretics or medications with a significant effect on renal function, as well as in patients with extracellular fluid deficit of any cause, e.g. during the peri- or post-operative phase of major surgery (see section 4.3). If Olfen is used in such cases, it is recommended to monitor kidney function as a precautionary measure. Upon discontinuation of therapy, pre-treatment conditions are usually re-established.

Haematologic effects

As with other NSAIDs, monitoring of the blood count is recommended during long-term treatment with Olfen/Olfen SR.

Like other NSAIDs, Olfen/Olfen SR may temporarily inhibit platelet aggregation. Patients suffering from a coagulation defect should be monitored carefully.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions may be observed with Olfen/Olfen SR and/or other diclofenac formulations.

Lithium

When used concomitantly, diclofenac may increase the plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin

When used concomitantly, diclofenac may increase the plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensives

Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensives (e.g. beta-blockers, angiotensin-converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effects. Such combinations should therefore be used with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly in the case of diuretics and ACE inhibitors, due to the increased risk of nephrotoxicity. As concomitant treatment with potassium-sparing diuretics may lead to hyperkalaemia, determination of serum potassium concentrations is necessary (see section 4.4).

Other NSAIDs and corticosteroids

Concomitant use of diclofenac and various systemic NSAIDs or glucocorticoids may promote the onset of undesirable gastrointestinal side effects (see section 4.4).

Anticoagulants and anti-platelet 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 isolated reports of an increased risk of haemorrhage in patients concomitantly receiving diclofenac and anticoagulants. Close monitoring of such patients is therefore recommended.

Selective serotonin re-uptake inhibitors (SSRIs)

Concomitant administration of systemic NSAIDs and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

Antidiabetic agents

Clinical studies have shown that diclofenac can be co-administered with oral antidiabetics without interfering with their clinical action. However, there have been isolated reports of hypoglycaemic and hyperglycaemic reactions after administration of diclofenac, which have required dosage adjustment of the antidiabetic agents. For this reason, monitoring of blood sugar levels is recommended as a precautionary measure during concomitant therapy.

Methotrexate

Caution is advised when administering NSAIDs within 24 hours before or after treatment with methotrexate, since methotrexate blood concentrations and methotrexate toxicity may be increased.

Ciclosporin

Like other NSAIDs the effect of diclofenac on renal prostaglandins can increase the nephrotoxicity of ciclosporin. It should therefore be given at doses lower than those in patients not receiving ciclosporin.

Quinolone antibiotics

There have been isolated reports of convulsions which are possibly the result of concomitant use of quinolones and NSAIDs.

4.6 Pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis can adversely affect pregnancy and/or embryofoetal development. Data from epidemiological studies indicate an increased risk of miscarriages, as well as cardiac malformations and gastroschisis, following use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is assumed to increase with the dose and duration of therapy.

Animal studies have shown that administration of a prostaglandin synthesis inhibitor results in increased pre- and post-implantation loss and embryofoetal mortality. Increased incidences of various malformations have also been reported, including cardiovascular malformations, in animals receiving a prostaglandin synthesis inhibitor during the organogenesis phase.

Diclofenac should not be given during the first and second trimesters of pregnancy unless absolutely necessary. If diclofenac is used by a woman who is attempting to conceive or during the first or second trimester, the dose should be kept as low as possible and the duration of treatment as short as possible.

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);
    - renal impairment, progressing to renal failure with oligohydramnios.
- expose mother and child to the following risks:
    - possible prolongation of the bleeding time, a platelet aggregation-inhibiting effect which can occur even at very low doses;
    - inhibition of uterine contractions, resulting in delayed or prolonged parturition.

Lactation

NSAIDs pass into breast milk. As a precaution, diclofenac should therefore not be taken by breast-feeding women. If treatment is essential, the infant should be switched to bottle feeding.

Fertility

The use of diclofenac may impair female fertility and is therefore not recommended in women wishing to conceive. In women who have difficulties in conceiving or who are undergoing investigation for infertility, withdrawal of diclofenac should be considered.

4.7 Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous disturbances while taking Olfen/Olfen SR should refrain from driving or using machines.

4.8 Undesirable effects

The following adverse effects include those reported with Olfen/Olfen SR and/or other diclofenac formulations, either in short-term or long-term use.

Frequency

"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)

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, nightmare, irritability, psychotic disorder.

Nervous system disorders

Common: headache, dizziness.

Rare: somnolence.

Very rare: paraesthesia, impaired memory, convulsions, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

Eye disorders

Very rare: visual disturbances, blurred vision, diplopia.

Ear and labyrinth disorders

Common: vertigo.

Very rare: tinnitus, impaired hearing.

Cardiac disorders

Very rare: palpitations, chest pain, cardiac insufficiency, myocardial infarction, hypertension.

Vascular disorders

Very rare: vasculitis.

Respiratory, thoracic and mediastinal disorders

Rare: asthma (including dyspnoea).

Very rare: pneumonitis.

Gastrointestinal disorders

Common: nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, cramps, flatulence, anorexia.

Rare: gastritis, gastrointestinal bleeding, haematemesis, bloody diarrhoea, melaena, gastric or intestinal ulcer (with or without bleeding or perforation).

Olfen Rectocaps: proctitis.

Very rare: colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease) constipation, stomatitis, glossitis, oesophageal lesion, diaphragm-like intestinal strictures, pancreatitis.

Olfen Rectocaps: exacerbation of haemorrhoids.

Olfen-75 SR Depotabs may cause chronic inflammatory conditions with pseudomembranes and strictures in the lower intestine (small and large intestine).

Hepatobiliary disorders

Common: transaminases increased.

Rare: hepatitis, jaundice, liver disorder.

Very rare: fulminant hepatitis, hepatic necrosis, hepatic failure.

Skin and subcutaneous tissue disorders

Common: rash.

Rare: urticaria.

Very rare: bullous rash, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), exfoliative dermatitis, alopecia, photosensitivity reactions, purpura, allergic purpura, pruritus.

Renal and urinary disorders

Common: fluid retention, oedema, hypertension.

Very rare: acute renal insufficiency, haematuria, proteinuria, interstitial nephritis, nephrotic syndrome, renal papillary necrosis.

General disorders and administration site conditions

Common: Olfen Rectocaps: local irritation.

Rare: oedema.

Clinical studies and epidemiological data indicate that diclofenac, particularly when used at high doses (150 mg daily) and for prolonged periods, is associated with an increased risk of arterial thrombo-embolic events (e.g. myocardial infarction or stroke) (see section 4.4).

4.9 Overdose

Symptoms

There is no known typical clinical picture following an overdose with diclofenac. An overdose can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures

Treatment of acute NSAID intoxication is essentially supportive or symptomatic.

In case of complications such as hypotension, renal failure, convulsions, gastrointestinal irritation and respiratory depression, supportive measures and symptomatic treatment should be carried out. Specific therapy, such as forced diuresis, dialysis or haemoperfusion, are presumably of little benefit in removing NSAIDs, due to their high protein binding rate 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: Antiinflammatory and antirheumatic product, non-steroid

ATC-code: M01AB05

Mechanism of action/Pharmacodynamics

Olfen contains the sodium salt of diclofenac, a nonsteroidal active substance having pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated experimentally, is thought to be important for the mechanism of action. Prostaglandins play an essential role in the development of inflammation, pain and fever. *In vitro*, at concentrations equivalent to levels reached in humans, Olfen does not induce suppression of proteoglycan biosynthesis in cartilage.

Clinical efficacy

The anti-inflammatory and analgesic properties become clinically evident in rheumatic disorders, in that the symptoms, such as pain at rest, pain on motion, morning stiffness, swelling of the joints, are significantly improved and functional ability increases. In post-traumatic/post-operative inflammations, Olfen causes a rapid reduction in spontaneous pain and pain on motion and reduces inflammatory swelling and wound oedema.

In moderate and severe non-rheumatic pain, a pronounced analgesic effect was also demonstrated in clinical trials. In cases of primary dysmenorrhoea, Olfen can alleviate pain and reduce the extent of bleeding.

Olfen (rectal capsule) also has a favourable effect on the symptoms of migraine attacks.

5.2 Pharmacokinetic properties

Absorption

Olfen-25/50 Lactab

Following gastric transit, diclofenac is rapidly and completely absorbed from the tablet, which is resistant to gastric juices. Although absorption rapidly occurs, its onset can be delayed due to the gastro-resistant coating of the tablet. Mean peak plasma concentrations of 1.5 µg/ml (5 µmol/l) are attained two hours following administration of 1 tablet of Olfen-50 Lactab. When taken during or after a meal, gastric transit is slower compared to the administration of a tablet before a meal. However, the amount of diclofenac absorbed remains equal.

Olfen-100 SR Depocaps, Olfen-75 SR Depotabs

Judging by the amount of unchanged diclofenac and its hydroxylated metabolites recovered in the urine, the amount of diclofenac released and absorbed from Olfen-100 SR Depocaps / Olfen-75 SR Depotabs is the same as that from the Olfen gastro-resistant tablets. Systemic availability of diclofenac from Olfen SR, however, is on average about 82 % of that obtained with the same dose of Olfen in the form of gastro-resistant tablets (possibly due to the release rate-dependent metabolism during the first passage through the liver). Due to the slower release of active substance from Olfen SR, lower peak plasma concentrations are attained than after administration of gastro-resistant tablets.

Mean peak plasma concentrations of 0.5 µg/ml and 0.4 µg/ml (1.6 and 1.25 µmol/l) are attained 4 hours after single-dose administration of 1 capsule of Olfen-100 SR Depocaps and 1 tablet of Olfen-75 SR Depotabs, respectively. Ingestion with food has no appreciable effect on the absorption and systemic availability of Olfen.

On the other hand, mean plasma concentrations of 13 ng/ml (40 nmol/l) are measured 24 h (16 h) after ingestion of 1 capsule of Olfen-100 SR Depocaps (1 tablet of Olfen-75 SR Depotabs).

Following ingestion of 1 capsule of Olfen-100 SR Depocaps once daily or 1 tablet of Olfen-75 SR Depotabs twice daily, trough plasma concentrations are about 22 ng/ml and 25 ng/ml (70 nmol/l and 80 nmol/l), respectively.

Olfen-50/100 Rectocaps

Absorption of diclofenac commences soon after administration of the rectal capsules, even if the absorption rate is slower than with the orally administered gastro-resistant tablet. Peak plasma concentrations are attained on average within an hour after administration of 1 rectal capsule of Olfen-50 Rectocaps, but the peak plasma concentrations per dosage unit are about two-thirds of the peak concentrations reached after administration of the gastro-resistant tablet.

Distribution

Diclofenac is 99.7 % 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.

Diclofenac passes into the synovial fluid, where maximum concentrations are measured 2 – 4 hours after peak plasma values have been obtained. The apparent elimination half-life from the synovial fluid is 3 – 6 hours. Already 2 hours after reaching maximal plasma level, the concentration of active substance is higher in the synovial fluid than in plasma, and it remain higher for up to 12 hours.

Metabolism

Biotransformation is partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are conjugated to glucuronic acid. Two of the phenolic metabolites formed are pharmacologically active, but 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 hours. Four of the metabolites, including the two active ones, also have short half-lives 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 % in unchanged form. The remainder of the dose is eliminated as metabolites via the bile in the faeces.

Kinetics in special patient groups

Relevant differences in absorption, metabolism and elimination due to patient age have not been observed.

In patients with impaired kidney function, no accumulation of unchanged active substance can be deduced from the kinetics of a single dose administered according to the usual dosage regimen. If 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 liver function (chronic hepatitis, compensated liver cirrhosis), kinetics and metabolism are the same as in patients with a healthy liver.

5.3 Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity and carcinogenicity studies with diclofenac, revealed no specific hazard for humans at the intended therapeutic doses. No teratogenic potential of diclofenac has been observed in mice, rats and rabbits.

In rats, diclofenac had no influence on the fertility of the parent animal. The pre-, peri-, and post-natal pup development was not affected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Olfen-25/50 Lactab

Tablet core

Sodium starch glycolate
Microcrystalline cellulose
Sodium stearyl fumarate
Colloidal anhydrous silica
Talc
Hypromellose

Coating (gastric juice resistant)

Methacrylic acid/ethyl acrylate copolymer (1:1), 30 % dispersion
Triethyl citrate
Talc

Coating (colour)

Hypromellose
Titanium dioxide E171
Talc
Quinoline yellow E104
Iron oxide yellow E172
Macrogol 6000

Olfen-75 SR Depotabs

Lactose monohydrate
Microcrystalline cellulose
Hypromellose
Talc
Magnesium stearate
Titanium dioxide E171
Iron oxide red E172
Macrogol 6000

Olfen-100 SR Depocaps

Capsule content

Lactose monohydrate
Microcrystalline cellulose
Microcrystalline cellulose and carmellose sodium
Glycerin trimyristate
Titanium dioxide E171
Ammonio, methacrylate copolymer dispersion, type B
Triethyl citrate
Silica colloidal, hydrated

Capsule shell

Gelatin
Titanium dioxide E171
Iron oxide black E172
Iron oxide red E172
Erythrosine E127

Olfen-50 Rectocaps

Triglycerides, medium chain
Triglycerides, hydrogenated, C_8-C_{18} (hard fat)
Soybean lecithin
Gelatin
Glycerol 85%
Titanium dioxide E171
Iron oxide yellow E172
Macrogol 20 000 (Polyethylene glycol 20 000)
Macrogol 1550 (Polyethylene glycol 1550)
Glycerol mono-oleate
Polyvinyl acetate
Talc

Olfen-100 Rectocaps

Triglycerides, medium chain
Triglycerides, hydrogenated, C_8-C_{18} (hard fat)
Soybean lecithin
Gelatin

Glycerol 85%
Titanium dioxide E171
Iron oxide red E172
Macrogol 20 000 (Polyethylene glycol 20 000)
Macrogol 1550 (Polyethylene glycol 1550)
Glycerol mono-oleate
Polyvinyl acetate
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Olfen-25 Lactab	5 years	
Olfen-50 Lactab:	Climatic zone I and II:	5 years
	Climatic zone III and IV:	4 years
Olfen-75 SR Depotabs:	3 years	
Olfen-100 SR Depocaps:	3 years	
Olfen-50 Rectocaps:	4 years	
Olfen-100 Rectocaps:	5 years	

6.4 Special precautions for storage

Olfen-25 Lactab:	Store dry below 25 °C	
Olfen-50 Lactab:	Climatic zone I and II:	Do not store above 25 °C
	Climatic zone III and IV:	Do not store above 30 °C
Olfen-75 SR Depotabs:	Store dry below 25 °C	
Olfen-100 SR Depocaps:	Climatic zone I and II:	Do not store above 25 °C
	Climatic zone III and IV:	Do not store above 30 °C
Olfen-50 Rectocaps:	Do not store above 25 °C	
Olfen-100 Rectocaps:	Climatic zone I and II:	Do not store above 25 °C
	Climatic zone III and IV:	Do not store above 30 °C

6.5 Nature and contents of container

Olfen-25/50 *Lactab*

The tablets are packed in PVC/PVDC-Aluminium blisters.

Olfen-25 Lactab: Packs of 10 and 30 tablets; hospital packs. Not all pack sizes may be marketed.

Olfen-50 Lactab: Packs of 10 and 20 tablets; hospital packs. Not all pack sizes may be marketed.

Olfen-75 SR Depotabs

The tablets are packed in PVC/PVDC/Aluminium blisters.
Packs of 10 and 30 tablets; hospital packs. Not all pack sizes may be marketed.

Olfen-100 SR Depocaps

The capsules are packed into blister strips.

Climatic zone I and II: PVC/PE/PVDC-Aluminium blisters

Climatic zone III and IV PVC/PE/PVDC-Aluminium blisters

Packs of 10 and 20 capsules; hospital packs. Not all pack sizes may be marketed.

Olfen-50/100 Rectocaps

The rectal capsules are packed in aluminium foil.

Olfen-50 Rectocaps: Packs of 10 rectal capsules; hospital packs. Not all pack sizes may be marketed.

Olfen-100 Rectocaps: Packs of 5 rectal capsules; hospital packs. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTORISATION NUMBER(S)

9. DATE OF THE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF THE REVISION OF THE TEXT

October 2009