

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 1 No of pages: 14 Ref.: 10.2014
--	---	--

Cardiovascular risk:

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with the duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (FDA, 2005);
- Diclofenac is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery (FDA, 2005);
- Gastrointestinal risk:
- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding ulceration and perforation of the stomach and intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (FDA, 2005).

1. Name of the medicinal product

Olfen™ - 25 / 50 Lactab™ film-coated tablets

Olfen™ - 75 SR Depotabs™ prolonged-release tablets

Olfen™ - 100 SR Depocaps™ prolonged-release capsules

2. Qualitative and quantitative composition

1 **Olfen - 25 / 50 Lactab** tablet contains 25 mg, 50 mg diclofenac sodium.

The other ingredients are: colouring agent: E 104 (quinoline yellow), excipient for coated tablet.

1 **Olfen - 75 SR Depotabs** tablet contains 75 mg diclofenac sodium.

The other ingredients are: excipient for coated tablet.

1 **Olfen - 100 SR Depocaps** capsule contains 100 mg diclofenac sodium.

The other ingredients are: colouring agent: E 127 (erythrosine), excipient for capsule.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Olfen™ - 25 / 50 Lactab™ - film-coated tablets

Ochre yellow, biconvex, film coated tablet, embossed “mp” on the one side and “O 25” or “O 50” on the other.

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

Pink / white opaque hard-gelatine capsules imprinted “100” filled with white to off-white pellets.

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.
- Acute gout attack (film-coated tablets).

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 2 No of pages: 14 Ref.: 10.2014
--	---	--

- As an adjuvant in acute painful inflammatory infections of the ears, nose or throat, e.g. pharyngotonsillitis, otitis (film-coated tablets).
- 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/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 “4.4 Special Warnings and precautions for use”).

Adults

Film-coated tablets (gastro-resistant)

The initial daily dose of Olfen Lactab film-coated tablets is generally 100-150 mg. For relatively mild cases and long-term treatment 75-100 mg/d is usually sufficient.

In general, the daily dose is divided into 2-3 single doses.

To avoid nocturnal pain and morning stiffness, administration of one Olfen Rectocap before bedtime can be combined with ingestion of film-coated tablets during the day (up to a maximum daily dose of 150 mg).

In primary dysmenorrhoea, the daily dose is generally 50-150 mg, individually adjusted; a starting dose of 50-100 mg should initially be selected and, if required, the dose can be increased over the course of several menstrual cycles up to a maximum of 150 mg/d.

The gastro-resistant sugar-coated tablets should be taken with some liquid, preferably before meals; they must not be divided or chewed.

Prolonged-release tablets, prolonged-release capsules

In general, the daily dose of Olfen Depocaps or Olfen Depotabs is 100–150 mg, i.e. one 100 mg prolonged-release capsule or two 75 mg prolonged-release tablets. For relatively mild cases and long-term treatment, one 75 mg or 100 mg prolonged-release tablet per day is generally sufficient. If the symptoms occur most severely during the night or in the morning, Olfen Depocaps or Olfen Depotabs should preferably be taken in the evening.

The prolonged-release capsules and prolonged-release tablets should be taken unchewed with some liquid, preferably with meals.

Special dosage instructions

Paediatric population

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.

Due to their active substance content, Olfen Lactab 50 mg film-coated tablets are not recommended for use in children. Olfen Lactab 25 mg film-coated tablets can be used in these patients. Olfen Depotabs 75 mg prolonged-release tablets and Olfen Depocaps 100 mg prolonged-release capsules are not suitable for children and adolescents.

Elderly patients (65 years and older)

An initial dose adjustment is not necessary in elderly patients (see “4.4 Special Warnings and precautions for use”).

Existing cardiovascular disease or significant cardiovascular risk factors

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 3 No of pages: 14 Ref.: 10.2014
--	---	--

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 “4.4 *Special Warnings and precautions for use*”).

Patients with renal insufficiency

Olfen is contraindicated in patients with renal insufficiency (see “4.3 *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 mild to moderate renal function impairment (see “4.4 *Special Warnings and precautions for use*”).

Patients with hepatic impairment

Olfen is contraindicated in patients with hepatic insufficiency (see “4.3 *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 “4.6 *Fertility, Pregnancy and 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 (creatinine clearance < 30 mL/min).
- 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 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

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 4 No of pages: 14 Ref.: 10.2014
--	---	--

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 Olfen (see “4.8 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 “4.5 Interactions with other medicinal products and other forms of interaction”).

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

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 “4.8 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 treatment with medicinal products containing low-dose acetylsalicylic acid (ASA) or other medicinal products likely to increase the gastrointestinal risk.

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 5 No of pages: 14 Ref.: 10.2014
--	---	--

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 “4.5 Interactions with other medicinal products and other forms of interaction”).

Hepatic effect

Close medical surveillance is necessary when prescribing Olfen Depocaps or Olfen Depotabs to patients with impaired hepatic function, since their condition may be exacerbated (see “4.8 Undesirable effects”).

As with all NSAIDs, including diclofenac, the levels of one or more liver enzymes may increase during treatment with Olfen Depocaps or Olfen Depotabs. 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 Depocaps or Olfen Depotabs therapy.

Olfen Depocaps or Olfen Depotabs 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 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 “4.3 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.

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 6 No of pages: 14 Ref.: 10.2014
--	---	--

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 Depocaps or Olfen Depotabs, as with other NSAIDs.

Like other NSAIDs, Olfen Depocaps or Olfen Depotabs can also temporarily inhibit platelet aggregation. Patients with a coagulation disorder should be closely monitored.

4.5 Interactions with other medicinal products and other forms of interaction

The following interactions have been observed with Olfen Depocaps or Olfen Depotabs and/or other pharmaceutical forms of diclofenac.

Reported interactions to be considered

Potent CYP2C9 inhibitors

Caution is recommended when administering diclofenac with potent CYP2C9 inhibitors (e.g. voriconazole). Significant increases in the peak plasma concentration of diclofenac and a general increase in the overall exposure to diclofenac following inhibition of diclofenac metabolism 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 "4.4 Special Warnings and precautions for use").

Ciclosporin

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

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 "4.4 Special Warnings and precautions for use").

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 7 No of pages: 14 Ref.: 10.2014
--	---	--

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 “4.4 Special Warnings and precautions for use”).

Anticoagulants and antiplatelet agents

Caution is recommended since concomitant administration could increase the risk of bleeding (see “4.4 Special Warnings and precautions for use”).

Although clinical trials do not appear to suggest that diclofenac influences the effect of anticoagulants, there have been isolated 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 “4.4 Special Warnings and precautions for use”).

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.

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 “5.3 Preclinical safety 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

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 8 No of pages: 14 Ref.: 10.2014
--	---	--

malformations, including cardiovascular abnormalities, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic phase (see “5.3 *Preclinical safety 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 Depocaps or Olfen Depotabs should refrain from driving or using machines.

4.8 Undesirable effects

The undesirable effects listed below include those reported with Olfen Depocaps or Olfen Depotabs and/or other pharmaceutical forms of diclofenac used for short-term or long-term treatment.

Frequency data

Very common ($\geq 1/10$), *common* ($\geq 1/100$ to $< 1/10$), *uncommon* ($\geq 1/1,000$ to $< 1/100$), *rare* ($\geq 1/10,000$ 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, 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

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 9 No of pages: 14 Ref.: 10.2014
--	---	--

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 or perforation).

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

Olfen-75 SR Depotabs 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 insufficiency, 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 "4.4 Special Warnings and precautions for use").

To report any side effect(s):

▪ **Saudi Arabia**

The National Pharmacovigilance and Drug Safety Centre (NPC)

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340
- Toll free phone: 8002490000
- E-mail: npc.drug@sfd.gov.sa
- Website: www.sfda.gov.sa/npc

4.9 Overdose

Symptoms

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 10 No of pages: 14 Ref.: 10.2014
--	---	---

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 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

ATC code: M01AB05

Mechanism of action

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

Film-coated tablets

Diclofenac is completely absorbed after passage of the gastro-resistant film-coated tablets through the stomach. Although absorption takes place rapidly, its onset may be delayed due to the gastro-resistant coating of the film-coated tablets. Mean peak plasma concentrations of 1.5 µg/mL are achieved, on average, two hours after administration of a 50 mg film-coated tablet. When a film-coated tablet is taken with or after a meal, passage through the stomach is slower than when the film-coated tablet is taken before a meal. However, the amount of absorbed diclofenac remains the same.

Prolonged-release capsules, prolonged-release tablets

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 Depocaps prolonged-release capsules and Olfen Depotabs prolonged-release tablets as from Olfen Lactab gastro-resistant film-coated tablets. However, the mean systemic availability of diclofenac from Olfen Depocaps or Olfen

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 11 No of pages: 14 Ref.: 10.2014
--	---	---

Depotabs is approximately 82% of that achieved with the same Olfen Lactab dose in the form of gastro-resistant film-coated 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 Depocaps or Olfen Depotabs, lower peak plasma concentrations are reached than after administration of gastro-resistant film-coated tablets.

Mean peak plasma concentrations of 0.5 µg/mL and 0.4 µg/mL are achieved, on average, four hours after administration of a 100 mg or 75 mg prolonged-release capsule/prolonged-release tablet with modified release. Ingestion with a meal has no appreciable effect on the absorption and systemic availability of Olfen Depocaps or Olfen Depotabs.

On the other hand, mean plasma concentrations of 13 ng/mL are measured 24 h (16 h) after ingestion of Olfen-100 SR Depocaps prolonged-release capsules (Olfen-75 SR Depotabs prolonged-release tablets 75 mg).

When Olfen Depocaps 100 mg prolonged-release capsules are taken once daily or Olfen Depotabs 75 mg prolonged-release tablets twice daily, trough plasma concentrations are about 22 ng/mL and 25 ng/mL, respectively.

The area under the concentration curve (AUC) after oral administration is about half as large as it is following parenteral administration, since only about half of the active substance undergoes first-pass hepatic metabolism. The kinetics do not change after repeat administration. Accumulation does not result when the recommended dosage intervals are maintained. Children reach similar plasma concentrations as adults after equivalent doses (mg/kg body weight).

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'-methoxy-diclofenac), 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.

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 12 No of pages: 14 Ref.: 10.2014
--	---	---

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 "4.3 Contraindications" and "4.6 Fertility, Pregnancy and 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

Olfen - 25 / 50 Lactab

Tablet core:

Sodium starch glycolate

Microcrystalline cellulose

Sodium stearyl fumarate

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 13 No of pages: 14 Ref.: 10.2014
--	---	---

Colloidal anhydrous silica

Talc

Hypromellose

Coating (gastro-resistant):

Methacrylic acid/ethyl acrylate copolymer 1:1

Triethyl citrate

Talc

Coating (colour):

Hypromellose

Titanium dioxide E171

Talc

Quinoline yellow E104

Iron oxide yellow E172

Macrogol 6000

Olfen - 75 SR Depotabs

Tablet core:

Lactose monohydrate

Cellulose microcrystalline

Hypromellose

Talc

Magnesium stearate

Coating:

Hypromellose

Titanium dioxide E171

Iron oxide red E172

Macrogol 6000

Olfen - 100 SR Depocaps

Capsule contents:

Lactose monohydrate

Microcrystalline cellulose

Carboxymethylcellulose 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

Printing ink:

Shellac Glaze-47.5 % (22 % esterified)

Iron oxide black E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Olfen - 25/50 Lactab - 60 Months

Olfen™ - 25 / 50 Lactab™ Olfen™ - 75 SR Depotabs™ Olfen™ - 100 SR Depocaps™	Summary of Product Characteristics	Page: 14 No of pages: 14 Ref.: 10.2014
--	---	---

Olfen - 75 SR Depotabs – 60 Months
Olfen - 100 SR Depocaps – 36 Months

6.4 Special precautions for storage

Store in the original package.

Keep out of the sight and reach of children.

Do not store above 30° C.

Do not use Olfen after the expiry date which is stated on the blister and carton after “EXP”. The expiry date refers to the last day of that month.

6.5 Nature and contents of container

Olfen - 25 Lactab

Packs: 10 and 30 tablets; hospital packs.

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

Not all pack sizes may be marketed.

Olfen - 50 Lactab

Packs: 10 and 20 tablets; hospital packs.

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

Not all pack sizes may be marketed.

Olfen - 75 SR Depotabs

Packs: 10 and 30 tablets; hospital packs.

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

Not all pack sizes may be marketed.

Olfen - 100 SR Depocaps

Packs: 10 and 20 capsules; hospital packs.

The capsules are packed into PVC/PE/PVDC-Aluminium blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

7. Marketing authorisation holder

Acino Pharma AG, Liesberg, Switzerland

8. Marketing authorisation numbers

Olfen™ - 100 SR Depocaps™: 7-222-95

Olfen™ - 25 Lactab™: 2-222-94

Olfen™ - 50 Lactab™: 3-222-94

9. Date of first Authorisation/ renewal of the authorisation

Olfen™ - 100 SR Depocaps™: 01.01.1995

Olfen™ - 25 Lactab™: 01.06.1994

Olfen™ - 50 Lactab™: 01.06.1994

10. Date of revision of the text

October 2014