

WARNING: RISK OF SERIOUS CARDIOVASCULAR and GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
- Olfen 75 mg IM, solution for injection is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Bleeding, Ulceration, and Perforation

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

1. Name of the medicinal product

OlfenTM 75 mg IM, solution for injection IM

2. Qualitative and quantitative composition

Active substances: diclofenac sodium, lidocaine hydrochloride.

Excipients: N-acetylcysteine, disodium edetate, macrogol 400, propylene glycol, sodium hydroxide, water for injections.

3. Pharmaceutical form

Solution for injection IM

Clear colourless to slightly yellow solution in 2 ml amber glass ampoules.

Each 2 ml ampoule contains diclofenac sodium 75 mg, lidocaine hydrochloride 20 mg.

4. Clinical Particulars

4.1 Therapeutic indications

Intramuscular injection

Initial treatment for the following conditions:

- Exacerbation of inflammatory or degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondyloarthritis, painful vertebral syndromes, extra-articular rheumatism.
- Acute attacks of gout.
- Renal and biliary colic.
- Pain, inflammation and swelling following injury and surgery
- Severe migraine attacks.

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 time for symptomatic control (see “Warnings and precautions”).

Adults

Treatment with Olfen ampoules should not last more than 2 days and can be continued, if necessary, with Olfen film-coated tablets or Olfen rectal capsules.

Intramuscular injection

The following instructions for intramuscular administration must be followed to avoid damage to nerves or other tissues at the injection site (which may lead to muscle weakness, muscle paralysis and hypoaesthesia).

The general dosage is one 75 mg ampoule/day, administered under aseptic conditions by deep intragluteal injection into the upper outer quadrant.

In severe cases (such as colic), two 75 mg ampoules/day may also be given exceptionally, by injecting one on the left side and one on the right side with an interval of a few hours in between. However, one 75 mg ampoule can also be combined with other pharmaceutical forms of Olfen (e.g. film-coated tablets, prolonged-release capsules, prolonged-release tablets, rectal capsules) up to a maximum total daily dose of 150 mg.

Clinical experience of use in migraine attacks is limited to the following procedure: initiation of treatment as early as possible with one 75 mg ampoule and, if necessary, continuation on the same day with rectal capsules at a dose of up to 75 mg. The total dose on the first day should not exceed 150 mg.

No data are available on the use of Olfen as a migraine treatment for duration of more than one day. Should treatment need to be continued on the following days, the daily dose should be limited to a maximum of 150 mg (as rectal capsules divided into single doses).

Intravenous infusion

Olfen must not be given as an intravenous bolus injection.

Special dosage instructions

Paediatric population (under 18 years)

Given their strength, Olfen ampoules are not suitable for use in children and adolescents.

Elderly patients (65 years and older)

In general, no adjustment of the initial dose is required in elderly patients. However, due to basic medical considerations, caution is advised in elderly patients. Particularly 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 m²) (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”).

Instructions for use

Olfen ampoules must be administered intramuscularly as a deep intragluteal injection in the upper outer quadrants. Each ampoule is intended for single use. The solution should be used immediately after opening. Any residual solution should be discarded.

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 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 insufficiency (GFR <15 ml/min/1.73 m²).
- Severe cardiac failure (NYHA III-IV).
- Patients with a high risk of postoperative bleeding, anticoagulation, incomplete haemostasis, haematopoietic disorders or cerebrovascular haemorrhage.
- Treatment of postoperative pain after coronary bypass surgery (or use of a heart-lung machine).

- Children under 14 years of age.

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 with the COX-1/COX-2 selectivity of the individual NSAIDs. Since no comparable clinical study data are currently available on 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. The lowest effective dose should be administered for the shortest possible duration also because of this risk.

The renal effects of NSAIDs comprise 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 Olfen (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

Due to its pharmacodynamic properties, Olfen – in common with other NSAIDs – may mask the signs and symptoms of an infection.

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”).

Due to basic medical considerations, caution is advised 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. The sodium metabisulfite contained in the ampoules can in isolated cases also trigger hypersensitivity reactions.

Respiratory effects (pre-existing asthma)

Reactions to NSAIDs, such as exacerbated asthma (referred to as analgesic intolerance/analgesic asthma), angioedema 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.

Particular caution is necessary when administering Olfen parenterally to patients who have bronchial asthma, since the symptoms can be exacerbated as a result.

Gastrointestinal effects

As with all NSAIDs, including diclofenac, close medical monitoring 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 for these patients, as well as for patients requiring concomitant low-dose acetylsalicylic acid (ASA) or other medicinal products that may 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 effects

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

As with other NSAIDs, including diclofenac, the levels of one or more liver enzymes may increase during treatment with Olfen. This has been reported very commonly (in approx. 15% of patients) in clinical trials of diclofenac, but is rarely accompanied by clinical symptoms. In the majority of these cases, the increases were marginal. Moderate increases (≥ 3 – < 8 times the upper limit of normal) were observed commonly (in 2.5%), 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.

Hepatitis can occur during diclofenac treatment 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 result commonly (in 1%–10%) 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, as with other NSAIDs.

Like other NSAIDs, Olfen 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 reported with Olfen ampoules 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 an overall increase in total exposure to diclofenac can occur.

CYP2C9 inducers

Caution is recommended when administering diclofenac with CYP2C9 inducers (e.g. rifampicin). A significant decrease in plasma concentrations and exposure may occur as a result of diclofenac.

Lithium

If used concomitantly, diclofenac can raise the plasma concentration of lithium. 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 impaired 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 organogenesis 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:

- o Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension; see also “Preclinical data”);

- o Impaired renal function, which may progress to renal failure with oligohydramnios;

– expose the mother and child to the following risks: o Possible prolongation of bleeding time, an inhibitory effect on platelet aggregation which may occur even at very low doses;

- o 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 infant should be switched to bottle feeding.

4.7 Effects on ability to drive and use machines

Patients who experience visual disturbances, drowsiness, dizziness, somnolence or other central nervous system disorders while taking Olfen should refrain from driving or using machines.

4.8 Undesirable effects

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

Frequencies

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 ($< 1/10,000$).

Infections and infestations

Very rare: Abscesses at the injection site.

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, drowsiness.

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, thoracic and mediastinal disorders

Rare: asthma (including dyspnoea).

Very rare: pneumonitis.

Gastrointestinal disorders

Common: nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, flatulence, decreased appetite.

Rare: gastritis, gastrointestinal bleeding, haematemesis, haemorrhagic diarrhoea, 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.

Hepatobiliary disorders

Common: transaminases increased.

Rare: hepatitis, jaundice, hepatic dysfunction.

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

Skin and subcutaneous tissue disorders

Common: skin rash.

Rare: urticaria.

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

Renal and urinary disorders

Common: fluid retention, oedema, hypertension.

Very rare: acute renal damage (acute renal failure), haematuria, proteinuria, tubulointerstitial nephritis, nephrotic syndrome, renal papillary necrosis.

Administration site reactions

Common: injection site reaction, injection site pain, injection site induration.

Rare: oedema, injection site necrosis.

* 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 an inhibition of the synthesis of prostaglandin and other similar substances that may 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.

To report any side effect(s):

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.sfd.gov.sa/npc

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, drowsiness, tinnitus or convulsions. Acute renal failure and hepatic damage may 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code: M01AB05

Mechanism of action/Pharmacodynamics

Olfen ampoules contain 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 essential to the mechanism of action. Prostaglandins play a considerable part 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 give rise to 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 decreases spontaneous and movement-induced pain, and reduces inflammatory swelling and wound oedema.

If combined with opioids as a treatment for postoperative pain, Olfen significantly reduces the need for opioids.

In clinical trials, the pronounced analgesic activity was also observed in moderate and severe non-rheumatic pain with an onset of effect within 15-30 minutes. Olfen was also found to have a favourable influence on the symptoms of migraine attacks.

Olfen ampoules are suitable as initial treatment for inflammatory and degenerative rheumatic diseases in particular, as well as for treatment of inflammatory, non-rheumatic pain.

5.2 Pharmacokinetic properties

Absorption

After intramuscular injection of 75 mg diclofenac, mean peak plasma concentrations of 2.5 µg/ml are reached after about 20 minutes. If diclofenac is given as an intravenous infusion of 75 mg for 2

hours, the mean peak plasma concentrations reach approx. 1.9 µg/ml. More rapid infusions result in higher peak plasma concentrations; slower infusions produce plateau concentrations proportional to the infusion rate after 3–4 hours.

Conversely, the plasma concentrations drop rapidly once they reach their peak following intramuscular injection or administration of gastro-resistant tablets or suppositories.

The area under the concentration curve (AUC) after intramuscular or intravenous administration of an equivalent dose is about twice as large as it is following oral or rectal administration, since only about half of the active substance undergoes first-pass hepatic metabolism after oral or rectal administration.

The kinetics do not change after repeat administration. Accumulation does not result when the recommended dosage intervals are maintained.

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 enters the synovial fluid. Here, maximum concentrations are measured 2–4 hours after the peak plasma concentrations have been reached. The apparent elimination half-life in synovial fluid is 3–6 h. As early as two hours after the peak plasma concentration is reached, the concentration of active substance in synovial fluid is higher than in the plasma and remains higher for up to 12 h.

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 takes place partly through glucuronidation of the intact molecule, but mainly through 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

The active substance is eliminated from the plasma with a systemic clearance of 263 ± 56 ml/min ($x \pm SD$). 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

The relationship between the plasma concentrations and dose is linear.

Kinetics in special patient groups

No relevant age-dependent differences have been observed in terms of absorption, metabolism or excretion of the medicinal product. In elderly patients, however, a 15-minute intravenous infusion produced plasma concentrations that were 50% higher than those expected based on the results obtained with young, healthy subjects.

In patients with impaired renal function, no accumulation of unchanged active substance can be inferred from the kinetics of a single dose in 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 cases 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 studies on monkeys. These reactions are suspected to be secondary to the ulcers observed in the gastrointestinal tract. In a 2-year study in rats treated with diclofenac, 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 2-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 observed 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

N-acetylcysteine, disodium edetate, macrogol 400, propylene glycol, sodium hydroxide, water for injections.

6.2 Incompatibilities

The Olfen 75 IM generally should not be mixed with other solutions for injection.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Period of use

The preparation must be administered immediately after reconstitution; discard any unused solution.

Special storage instructions

Do not store above 30°C.

Store the Olfen 75 IM in the original package in a dry place.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

The product is filled into 2 ml amber (brown) glass ampoules (hydrolytic class I), with white OPC (One Point Cut) point.

Packs of 3 and 5 ampoules of 2 ml; hospital packs.

Not all pack sizes may be marketed.

7. Marketing Authorisation Holder

Acino Pharma AG, Liesberg (Switzerland)

8. Marketing Authorisation Number(s)

8-222- 95

9. Date of first authorisation/renewal of the authorization

1995

10. Date of revision of the text

July 2018