INFORMATION FOR THE MEDICAL PROFESSION

GROFENAC® ampoules

Composition

Active substance: diclofenac sodium
Excipients: mannitolum, propylene glycol, antioxidant: sodium metabisulphite (E223) 9.0mg
Preservative: benzyl alcohol 120mg, water for injection – sufficient for a 3ml solution

Galenical form and quantity of active ingredient per unit

1 ampoule (3ml) contains: diclofenac sodium = 75mg

Indications/possible uses as intramuscular injection

Exacerbation of inflammatory or degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondylarthritis, painful vertebral syndrome, extra-articular rheumatism.
Acute episodes of gout.
Renal and biliary colic.
Pain, inflammation and swelling after injury and surgical intervention.
Severe migraine attacks.

Dosage/administration

As a general recommendation, the dose should be adjusted individually and the lowest effective dose should be administered over the shortest possible time.

Adults:
Treatment with Grofenac injection solution should not last more than 2 days and may, if necessary, be continued with Grofenac tablets or suppositories.

Intramuscular injection:
The following instructions should be followed for intramuscular administration in order to avoid nerve or other tissue damage at the injection site.

The dosage is generally 1 ampoule of 75 mg/d, which is injected deep into the upper outer quadrants.

In severe cases (e.g. colic) 2 ampoules of 75 mg/d may be given by way of exception, one each on the left and right sides and with an interval of a couple of hours.

However one ampoule of 75 mg may also be combined with other forms of administration of Grofenac (e.g. coated tablets, suppositories) up to a maximum daily dose of 150 mg in total.

Clinical experience is confined to the following procedure for use with migraine attacks: treatment is started as early as possible with one ampoule of 75 mg and if necessary continued with suppositories in a dose of up to 100 mg on the same day. The total dose on the first day should not exceed 175 mg. There is no information about the use of Grofenac for migraine with treatment periods of more than one day. If a continuation of the treatment should be necessary the next day, the maximum daily dose is to be confined to 150 mg (in the form of suppositories and divided into single doses).

Children and young people:
Due to the strength of the dose, Grofenac injectable solution is not suitable for children and young people.

Contraindications

Known hypersensitivity to the active ingredient or one of the excipients according to the composition.
History of allergic diseases (such as bronchospasm, acute rhinitis, mucous polyps of the nose, urticaria) after taking acetylsalicylic acid or other non-steroidal antirheumatics (NSARs).
In the last trimester of pregnancy (cf. "Pregnancy/Lactation").
Active gastric and/or duodenal ulcer, gastrointestinal bleeds or perforation.
Inflammatory intestinal disease such as Crohn's disease or ulcerative colitis.
Severe cardiac insufficiency (NYHA III-IV).
Severe liver function disorder (Child-Pugh Class C) (cirrhosis of the liver and ascites).
Moderate and severe renal insufficiency (creatinine clearance <50 ml/min), hypovolaemia or dehydration.
Patients with a high risk of post-operative bleeding, anticoagulation, incomplete haemostasis, blood count disorders or cerebrovascular bleeding.
Treatment of post-operative pain after a coronary bypass operation (or use of a heart-lung machine).
Children under 14 years of age.

Warnings and special precautions for use

General warnings for the use of systemic non-steroidal anti-rheumatics:
Gastrointestinal ulceration, bleeding or perforations may occur at any time during treatment with non-steroidal anti-rheumatics (NSARs), COX-2 selective or otherwise, even without warning symptoms or anamnestic indicators. In order to reduce this risk, the smallest effective dose should be administered for the shortest possible treatment period.

Warnings:
An increased risk of thrombotic cardiovascular and cerebrovascular complications has been shown in placebo-controlled studies for certain selective COX-2-inhibitors. It is not yet known whether this risk correlates directly with the COX-1/COX-2 selectivity of the individual NSAR. Since there are currently no comparable clinical study data for diclofenac with maximum dosage and long term therapy, a similarly increased risk cannot be ruled out. Until the appropriate data are available, diclofenac should only be used in clinically confirmed coronary heart disease, cerebrovascular disease, peripheral arterial occlusive disease or in patients with high risk factors (e.g. high blood pressure, hyperlipidaemia, diabetes mellitus, smoking) after careful evaluation of the risk-benefit ratio. Also, because of this risk, the smallest effective dose should be administered for the shortest possible treatment period.
The renal effects of NSARs include fluid retention with oedema and/or arterial hypertonia. Diclofenac sodium should therefore only be used with care in patients with impaired cardiac function and other conditions which predispose to fluid retention. Care is also necessary with patients who are taking diuretics or ACE-inhibitors at the same time, and where there is an increased risk of hypovolaemia. The consequences are generally more serious in elderly people. If patients on Grofenac – treatment experience gastrointestinal bleeding or ulcerations, the product should be withdrawn.
There have been very rare reports of serious, sometimes fatal skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis in association with the use of NSARs including Grofenac (cf. "Undesirable effects"). The risk to the patients seems to be greatest at the start of the treatment; the reaction usually sets in within the first month of treatment. Grofenac should be withdrawn at the first signs of a skin eruption, mucous membrane lesions or other signs of hypersensitivity.
As with other NSARs, allergic reactions, including anaphylactic/anaphylactoid reactions, may occur in rare cases even without prior exposure to diclofenac.
Owing to its pharmacodynamic properties, Grofenac – like other NSARs – may mask the signs and symptoms of an infection.

Precautionary measures
General
The simultaneous use of Grofenac and systemic NSARs such as cyclo-oxygenase-2 selective inhibitors is to be avoided since there are no indications of a synergetic benefit but there is potential for additional undesirable effects.
In patients of advanced age, care is advisable for fundamental medical reasons. Above all, it is recommended that the lowest effective dose should be used in frail, elderly patients or those with a low bodyweight.
The sodium metabisulphite contained in the ampoules may also trigger isolated hypersensitivity reactions.

Pre-existing asthma
In patients with asthma, seasonal allergic rhinitis, chronic obstructive pulmonary disease or chronic infections of the respiratory tract (particularly if these are associated with allergic rhinitis-like symptoms), reactions to NSARs such as exacerbations of the asthma (so-called analgaesic intolerance/analgaesic asthma), Quincke's oedema or urticaria are more common than in other patients. Particular caution is therefore advised with these patients (emergency readiness). This also applies to patients who, for instance, have an allergic reaction such as skin eruption, pruritus or urticaria to other substances.
Special caution is advisable if Grofenac is administered parenterally to patients who suffer from bronchial asthma, since this can aggravate the symptoms.

Gastrointestinal effects
As with all NSARs, close medical monitoring is recommended and particular care should be applied in prescribing Grofenac to patients with symptoms which suggest gastrointestinal (GI) disorders or patients with signs of gastric or intestinal ulceration, bleeding or perforation in their history (cf. "Undesirable effects"). The risk of GI-bleeds is greater with higher doses of NSARs and also in patients with a history of ulcers, particularly where there are additional complications of bleeding or perforation and in elderly patients.
In order to reduce the risk of GI-toxicity in patients with a history of ulcers, particularly where there are additional complications of bleeding or perforation and in elderly patients, treatment should be started and maintained at the lowest effective dose.
The combination treatment with protective substances (e.g. proton pump inhibitors or misoprostol) should be considered for these patients and also for patients who simultaneously need medication which contains low doses of acetylsalicylic acid (ASS)/aspirin or other medicinal products which may possibly increase the gastrointestinal risk.
Patients with a history of GI-toxicity, particularly elderly patients, should report all unusual abdominal symptoms (in particular GI-bleeding). Care is recommended with patients who at the same time are receiving medicinal products which may raise the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, antithrombotics or selective serotonin-reuptake inhibitors (cf. "Interactions").

Hepatic effects
Close medical monitoring is needed if Grofenac is administered to patients with impaired hepatic function, since their disease may be aggravated (cf. "Undesirable effects").
As also with other NSARs, the levels of one or more hepatic enzymes may rise during treatment with Grofenac. This has very frequently been seen with diclofenac in clinical studies (in about 15% of patients), but is rarely accompanied by clinical symptoms. In the majority of these cases, the rises are borderline. Frequently (in 2.5%), moderate rises have been observed (≥3–<8× the upper normal limit) whilst the incidence of clear rises (≥8× the upper normal limit) remain in the range of about 1%. In 0.5% of the abovementioned clinical studies, there was clinically manifest liver damage as well as increases in hepatic enzymes. The enzyme rises were generally reversible after withdrawal of the product.

Renal effects
Owing to the important function of prostaglandin in maintaining the renal blood supply, oedema and hypertonia occur frequently (1–10%) during long-term therapy with high dose NSARs.

Special care is required with patients with impaired cardiac or renal function, a history of hypertonia, elderly patients, patients who are being treated at the same time with diuretics or medicinal products which may significantly affect renal function, and patients with marked fluid deficiency in the extracellular area for whatever reason, e.g. before or after major surgical intervention (cf. "Contraindications"). As a precautionary measure, it is recommended that renal function be monitored if Grofenac is used in such cases. After withdrawal of the therapy, the patient usually recovers to the condition they were in before the treatment.

Haematological effects
As with other NSARs, blood tests are recommended during long-term treatment with Grofenac.
Like other NSARs, Grofenac may also temporarily inhibit thrombocyte aggregation. Patients with a coagulation disorder should be carefully monitored.

Interactions
The following interactions may be observed with Grofenac injection solution and/or other forms of administration of diclofenac.

Lithium
With concomitant use, diclofenac may raise the plasma concentration of lithium. A check on the lithium level in the serum is recommended.

Digoxin
With concomitant use, diclofenac may raise the plasma concentration of digoxin. A check on the digoxin level in the serum is recommended.

Diuretics and antihypertonics
As with other NSARs, the simultaneous use of diclofenac and diuretics or antihypertonics (e.g. beta-blockers, angiotensin-converting enzyme [ACE] inhibitors) may lead to a reduction in their antihypertonic effects. Therefore a combination should be used with care and in patients, particularly elderly ones; blood pressure should be checked regularly. The patients should be suitably hydrated and, at the start of combination treatment and regularly thereafter, care should be taken to check renal function, particularly with diuretics and ACE inhibitors, since here there is an increased risk of nephrotoxicity. Simultaneous treatment with potassium-preserving medicinal products may lead to raised potassium levels in the serum, which should therefore be checked frequently (cf. "Warnings and special precautions for use").

Other NSARs and corticosteroids
The simultaneous administration of diclofenac with other systemic NSARs or corticosteroids may increase the frequency of undesirable gastrointestinal effects (cf. "Warnings and special precautions for use").

Anticoagulants and antithrombotics
Care should be taken, as simultaneous administration may increase the risk of bleeding (cf. "Warnings and special precautions for use").
Although clinical trials do not seem to offer any grounds to suggest that diclofenac influences the effect of anticoagulants, there are isolated reports of an increased risk of bleeding with the simultaneous use of diclofenac and anticoagulants. Careful monitoring is therefore recommended in these cases.

Selective serotonin-reuptake inhibitors (SSRIs)
Simultaneous administration of systemic NSARs and SSRIs may increase the risk of gastrointestinal bleeding (cf. "Warnings and special precautions for use").

Antidiabetics
Clinical trials have shown that diclofenac can be given together with oral antidiabetics without affecting their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic reactions after the administration of diclofenac, which have required the antidiabetic dosage to be adjusted. For this reason, a check on the blood sugar level is recommended as precautionary measure during combination therapy.

Methotrexate
Care should be taken if NSARs are administered less than 24 hours before or after treatment with methotrexate, since the methotrexate level in the blood and the toxicity of the methotrexate may be increased.

Cyclosporin
Diclofenac, like other NSARs, can reinforce the nephrotoxicity of cyclosporin owing to its effects on renal prostaglandins. Therefore it should be administered in lower doses than in patients not receiving cyclosporin.

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

Pregnancy/Lactation

Pregnancy:
The use of diclofenac for pregnant women has not been studied.
Animal experiment studies have not shown any direct or indirect toxicity affecting pregnancy, embryonic development, development of the foetus, the birth and/or postnatal development (cf. "Preclinical data").

1st and 2nd trimester: Grofenac injection solution should only be used during the first and second trimester if there is a compelling indication and then only in the lowest effective dose.
3rd trimester: as with other NSARs, Grofenac injection solution is contraindicated in the 3rd trimester of pregnancy owing to possible premature occlusion of the ductus arteriosus (Botallo's duct) and/or possible tocolysis (cf. "Contraindications").

Lactation
Like other NSARs, diclofenac passes into the mother's milk in small quantities. For this reason and in order to avoid undesirable effects on the infant, Grofenac should not be used during lactation. If the treatment is indispensable, the infant should be switched to bottle feeding.

Fertility:
Like other NSARs, Grofenac injection solution may affect female fertility; its administration to women wanting to have children is not recommended. The withdrawal of Grofenac injection solution should be considered for women who have difficulties in conceiving or who are being investigated for infertility.

Effect on ability to drive and operate machines

Patients who experience vision disorders, confusion, dizziness, drowsiness or other central nervous disorders while on Grofenac should avoid driving a vehicle or operating machines.

Undesirable effects

The following undesirable effects comprise those which have been reported with Grofenac injection solution and/or other pharmaceutical forms of diclofenac during short or long-term treatment.

Frequency
Very common (>1/10), common (>1/100 <1/10), occasional (>1/1000 <1/100), rare (>1/10,000 <1/1000), very rare (<1/10,000).

Infections
Very rare: abscesses at the injection site.
Blood and lymphatic system
Very rare: thrombocytopaenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system
Rare: hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotonia and shock).
Very rare: angioneurotic oedema (including facial oedema).
Psychiatric disorders
Very rare: disorientation, depression, insomnia, nightmares, irritability, psychotic disorders.
Nervous system
Common: headaches, confusion.
Rare: drowsiness.
Very rare: paraesthesia, memory impairment, convulsions, anxiety, shivering, aseptic meningitis, altered taste sensations, cerebrovascular accidents.
Eyes
Very rare: vision disorders, clouded vision, diplopia.
Ear and inner ear
Common: vertigo
Very rare: tinnitus, impaired hearing.
Heart
Very rare: palpitations, chest pains, cardiac insufficiency, infarction, hypertonia.
Vascular
Very rare: vasculitis.
Respiratory tract
Rare: asthma (including dyspnoea).
Very rare: pneumonitis.
Gastrointestinal disorders
Common: nausea, vomiting, diarrhoea, stomach pains, dyspepsia, flatulence, anorexia.
Rare: gastritis, gastrointestinal bleeding, haematemesis, haemorrhagic diarrhoea, melaena, gastrointestinal ulcer (with or without bleeding or perforation).
Very rare: colitis (including haemorrhagic colitis and exacerbation of colitis ulcerosa or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorders, diaphragm-like intestinal strictures and pancreatitis.
Liver and gall bladder
Common: raised transaminase levels.
Rare: hepatitis, jaundice, hepatic function disorders.
Very rare: fulminating hepatitis.
Skin
Common: skin eruptions.
Rare: urticaria.
Very rare: bullous rashes, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), exfoliative dermatitis, hair loss, photosensitivity, purpura, allergic purpura, pruritus.
Kidneys and urinary tract
Common: fluid retention, oedema, hypertonia.
Very rare: acute renal insufficiency, haematuria, proteinuria, interstitial nephritis, nephrotic syndrome, renal papillary necrosis.
Reactions at the application site
Common: reaction at the injection site, pain at the injection site, hardening at the injection site.
Rare: oedema, necrosis at the injection site.

Clinical studies and epidemiological data indicate that the use of diclofenac, particularly in high doses (150 mg daily) and in long-term use may be associated with an increased risk of arterial thromboembolic events (e.g. myocardial infarction or stroke) (cf. "Warnings and special precautions for use").

Overdose

Symptoms
There is no typical clinical picture after an overdose of diclofenac. An overdose may trigger symptoms such as vomiting, gastrointestinal bleeding, diarrhoea, confusion, tinnitus or convulsions. In the case of serious intoxication, there may be acute kidney failure and liver damage.

Therapeutic measures
The treatment of an acute intoxication with an NSAR consists mainly of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be applied for complications such as hypotonia, kidney failure, convulsions, gastrointestinal problems and respiratory depression.
Specific measures such as forced diuresis, dialysis or haemoperfusion are probably not helpful for the elimination of NSARs owing to their high protein binding and extensive metabolization.

Properties/Effects

ATC-Code: M01AB05

Effects/Pharmacodynamics

Grofenac injection solution contains diclofenac sodium, a non-steroidal active substance with marked anti-rheumatic, anti-inflammatory, analgaesic and fever-relieving properties.
The inhibition of prostaglandin biosynthesis is considered important to the mechanism, and this has been demonstrated in experiments. Prostaglandins play a significant part in the occurrence of inflammation, pain and fever.
In concentrations which correspond to the levels reached in humans, Grofenac in vitro does not cause any suppression of the biosynthesis of proteoglycans in the cartilage.

Clinical efficacy
In the treatment of rheumatic disease, the anti-inflammatory and analgaesic properties produce a significant improvement in problems such as resting pain, pain on moving, morning stiffness, joint swelling and also an increase in functional capacity.
With post-traumatic and post-operative inflammations, Grofenac produces a rapid decrease in spontaneous and movement-related pain and reduces the inflammatory swelling or wound oedema.
When used together with opioids for the treatment of post-operative pain, Grofenac significantly reduces the need for opioids.
In clinical trials, a marked analgaesic effect has also been demonstrated in moderate and severe pain conditions of a non-rheumatic nature, and there the effect occurred within 15–30 minutes.
It has also been shown that Grofenac has a beneficial effect on the symptoms of migraine attacks.
Grofenac injection solution is particularly suitable as initial therapy for inflammatory and degenerative rheumatic disease and the treatment of inflammatory pain conditions of a non-rheumatic nature.

Pharmacokinetics

Absorption
After intramuscular injection of 75 mg diclofenac, maximum plasma concentrations of an average of 2.5 µg/ml (8 µmol/l) are reached after about 20 minutes. The plasma concentrations are in linear proportion to the dose.
In contrast, the plasma concentrations drop rapidly as soon as they have reached their maximum after intramuscular injection or the administration of tablets with gastric-juice resistant coatings or suppositories.
The area under the concentration curve (AUC) after intramuscular injection is roughly twice as large as after oral or rectal application, because after oral or rectal application the active substance is roughly half metabolised during the first hepatic passage ("first pass").
The kinetics do not change with repeated administration. There is no accumulation if the recommended dose interval is observed.

Distribution
Diclofenac is 99.7% bound to the serum proteins, chiefly to albumin (99.4%).
The apparent distribution volume can be calculated, and according to calculation is 0.12–0.17 l/kg.
Diclofenac penetrates the synovial fluid. The maximum concentrations there are measured 2–4 hours after reaching the maximum plasma values. The apparent half-life for elimination from the synovial fluid is 3–6 hours. Just two hours after reaching the maximum plasma concentration, the concentration of the active substance in the synovial fluid is higher than in the plasma and remains higher for up to 12 hours.

Metabolism
Biotransformation takes place partly through glucuronidation of the intact molecule but chiefly by single and multiple hydroxylation and methoxylation. This results in several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy- und 3'-hydroxy-4'-methoxy-diclofenac), which are mostly conjugated to glucuronic acid. Two of these phenolic metabolites are pharmacologically active, although far less than diclofenac.

Elimination
The elimination of the active substance from the plasma takes place with systemic clearance of 263 ± 56 ml/min (x ± SD). The terminal half-life is 1–2 hours.
Four of the metabolites, including the two active metabolites, have a short half-life of 1–3 hours. The virtually inactive metabolite 3'-hydroxy-4'-methoxy-diclofenac has a significantly longer half-life.
About 60% of the dose administered is excreted renally in the form of metabolites, and less than 1% as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Kinetics in special patient groups
No significant age-related differences in the absorption, metabolization or elimination of the product have been observed.
In patients with impaired renal function, no accumulation of the unchanged active substance can be inferred from the kinetics of a single dose for the customary dosage schedule. With creatinine clearance of less than 10 ml/min, the calculated steady state plasma levels of the metabolites are approximately four times higher than in healthy subjects. However the metabolites are ultimately cleared through the bile.
With impaired liver function (chronic hepatitis, compensated cirrhosis of the liver) the kinetics and metabolization of diclofenac are similar to those in patients with a healthy liver.

Preclinical data
Preclinical data from studies of acute toxicity and toxicity after multiple doses, and of the genotoxicity, mutagenicity and carcinogenicity of diclofenac have not produced any indication of a particular danger to humans with the intended therapeutic doses. There are no indications in mice, rats or rabbits of any teratogenic potential for diclofenac.
For rats, diclofenac had no influence on the fertility of the parent animals. The prenatal, perinatal and postnatal development of the offspring was not affected.

Other information

Shelf life:
The product should only be used up to the "EXP" date shown on the container.

Instructions for handling:
Each ampoule is intended for a single use. The solution is to be used immediately after opening. Any residual quantities must be thrown away.

Special instructions for storage:
Store at room temperature (15-25°C) and out of reach of children.

No. of authorisation

47'835 (Swissmedic)

Packaging

1 pack of 5 Grofenac ampoules à 3ml. (B)

Authorisation holder

Dr. Grossmann AG Pharmaca - 4127 Birsfelden-Basel/ Switzerland

Last revised in
October 2009.

2600012/b 292 1500 2