Information for Healthcare Professionals

Novartis Pharma **FLOTAC®**

1. Name of the medicinal product

FLOTAC®
145.6 mg diclofenac colestyramine (equivalent to 75 mg diclofenac sodium), hard gelatin capsules

2. Qualitative and quantitative composition

1 hard capsule contains 145.6 mg diclofenac colestyramine (equivalent to 75 mg diclofenac sodium).

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Hard gelatin capsules

4. Clinical particulars

4.1 Therapeutic indications

FLOTAC® is indicated for adults (18 years and older).

Symptomatic treatment of pain and inflammation in cases of:
- Acute arthritis (including gout attacks);
- Chronic arthritis, especially in rheumatoid arthritis (chronic polyarthritis);
- Ankylosing spondylitis (Bechterew's disease) and other inflammatory rheumatic diseases of the vertebral column;
- Irritation in cases of osteoarthritis and spondylarthritis;
- Inflammatory rheumatic soft-tissue diseases;
- Painful swelling or inflammation following injuries or surgery.
- Tumour pain, especially when the skeleton is affected or in cases of inflammatory peritumoural oedema

Note on use following operations
FLOTAC® is indicated only for use after surgery in patients whose preoperative history shows no increased haemorrhagic diathesis, no impaired renal function and no evidences of gastric or intestinal ulcers. Particularly following major surgical interventions with high blood and fluid loss, it may be used only if renal excretion has normalised postoperatively.

4.2 Posology and method of administration

The recommended dosage range of FLOTAC® for adults is from 1 up to a maximum of 2 hard capsules per day, depending on the severity of the disease.
If appropriate, adults should receive 1 hard capsule of FLOTAC® twice a day. The

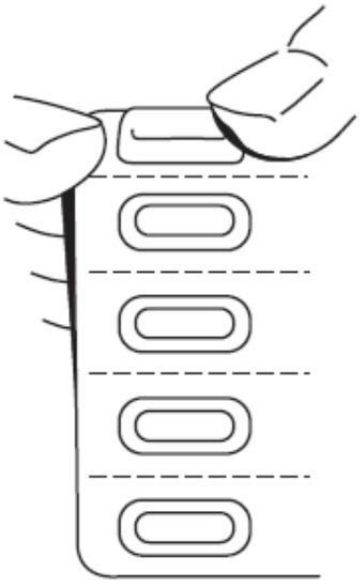
daily dose is divided into two single doses.
For milder cases and in long-term treatment, 1 hard capsule a day is often sufficient.

Method and duration of administration
FLOTAC® is swallowed whole with plenty of liquid. For patients with a sensitive stomach, it is recommended that FLOTAC® be taken during meals. The hard capsule must not be divided.

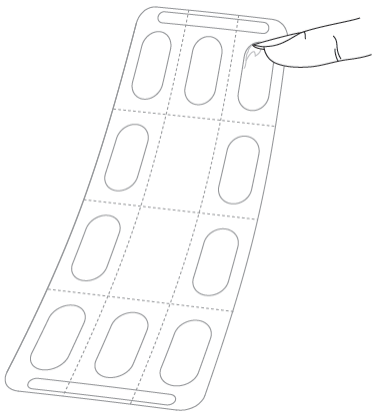
The duration of use is decided by the treating physician.
For rheumatic diseases, it may be necessary to take FLOTAC® over a longer period.

Undesirable effects can be reduced by using the lowest effective dose over the shortest period of time required to control symptoms (see section 4.4).

It is recommended to press on either of the rounded ends of the blister (see illustration) in order to avoid damaging the capsules when expelling them from the push-through pack.



If you are not able to extract the capsules from the blister cup as mentioned above, it is recommended that you use your fingernail to pierce the blister carefully ensuring that the capsule is not damaged in doing so.



Special patient groups
Elderly patients (aged 65 years or above)
In general, no dosage adjustment is necessary for elderly patients (see section 4.4). For medical reasons, caution is indicated especially in elderly patients who are frail or with low body weight.

Impaired renal function
Flotac® is contraindicated in patients with severe renal failure (GFR <15 mL/min/1.73m^2). No dose reduction is necessary in patients with mild to moderate impairment of renal function (for patients with severe renal insufficiency, see section 4.3).

Impaired hepatic function
No dose reduction is necessary in patients with mild to moderate impairment of hepatic function (for patients with severe hepatic dysfunction, see section 4.3).

Paediatric population (below 18 years of age)
FLOTAC® is not suitable for children and adolescents, as the active substance content is too high and/or due to the lack of individual dosing.

4.3 Contraindications

FLOTAC® must not be used in cases of:
- Hypersensitivity to the active substance or to any of the excipients;
- Known reactions in the form of bronchospasm, asthma, rhinitis or urticaria following intake of acetylsalicylic acid or other non-steroidal antirheumatic/anti-inflammatory agents (NSAIDs) in the past;
- Unexplained haematopoietic disorders;
- Existing or past history of recurrent peptic ulcers or haemorrhage (at least 2 separate episodes of confirmed ulceration or bleeding);
- History of gastrointestinal bleeding or perforation associated with previous therapy with NSAIDs;
- Cerebrovascular or other active bleeding;
- Severe hepatic dysfunction (see section 4.4);
- Severe renal dysfunction (GFR <15 mL/min/1.73m^2) (see section 4.4);
- The last trimester of pregnancy (see section 4.6);
- Paediatric population;
- Known heart failure (NYHA II-IV), ischaemic heart disease, peripheral arterial occlusive disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

<u>Gastrointestinal effects</u>
The use of FLOTAC® in combination with NSAIDs, including selective cyclooxygenase-2-inhibitors, should be avoided, as there is no evidence of a synergistic effect and the undesirable effects may possibly be potentiated.

Undesirable effects can be reduced by using the lowest effective dose for the shortest possible time needed to control symptoms (see section 4.2 and gastrointestinal and cardiovascular effects below).

Elderly patients
Undesirable effects are more common in elderly patients on NSAID therapy, including diclofenac, especially gastrointestinal bleeding and perforations, which may have a fatal outcome (see section 4.2). It is recommended that the lowest effective dose be used in elderly patients who are frail or have a low body weight.

Gastrointestinal bleeding, ulcers and perforations
NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

Gastrointestinal bleeding, ulcers or perforations, including those with a fatal outcome, have been reported with all NSAIDs, including diclofenac. They have occurred at any point during therapy, with or without prior warning symptoms or a history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is greater with increasing NSAID doses, in patients with a history of ulcers, especially with complications of bleeding or perforation (see section 4.3), and in elderly patients. These patients should begin treatment at the lowest available dose.

For these patients and for patients who require concomitant therapy with low-dose acetylsalicylic acid (ASA) or other medicinal products which can increase gastrointestinal risk (see section 4.5), combined therapy with protective medicinal products (e.g. misoprostol or proton pump inhibitors) should be considered (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, especially those of advanced age, should report any unusual symptoms in the abdominal cavity (especially gastrointestinal bleeding) particularly at the start of therapy.

Caution is advisable if patients are concomitantly receiving medicinal products that may increase the risk of ulcers or bleeding e.g. oral and systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as ASA (see section 4.5).

Treatment must be discontinued if gastrointestinal bleeding or ulcers occur in patients on FLOTAC®.

NSAIDs, including diclofenac, should only be used with caution in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may deteriorate (see section 4.8).

Cardiovascular effects
Appropriate monitoring and counselling of patients with a history of hypertension and/or mild-to-moderate heart failure (NYHA I) is required, as fluid accumulation and oedema have been reported in connection with NSAID therapy including diclofenac.

Clinical studies and epidemiological data consistently indicate that the use of diclofenac is associated with increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke) particularly at a high dose (150 mg daily) and in long-term treatment (see section 4.3).

Patients with significant risk factors (e.g. hypertension, hyperlipidaemia, diabetes, smoking) for cardiovascular events should be treated with diclofenac only after careful assessment. Because the cardiovascular risks of diclofenac may increase with dose and duration of administration, the lowest effective daily dose should be used for the shortest possible time. The patient's need for symptomatic-relief and response to therapy should be re-assessed regularly.

Patients should be alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurred speech), which may occur without warning. Patients should be advised to contact a doctor immediately in the case of such an event.

Skin reactions
In very rare cases, serious skin reactions, some with a fatal outcome, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) (see section 4.8), have been reported with NSAID therapy, including diclofenac. The risk of such reactions appears to be greatest at the start of therapy, as these reactions have occurred within the first month of treatment in the majority of cases. FLOTAC® should be discontinued at the first signs of rash, mucosal lesions or other signs of hypersensitivity reaction.

Hepatic effects
Careful medical supervision is required in patients with hepatic dysfunction, as their condition might deteriorate.
As with other NSAIDs, including diclofenac, one or more liver enzyme values may increase. If FLOTAC® is taken for prolonged periods or repeatedly, regular monitoring of hepatic function is indicated as a precaution. FLOTAC® should be discontinued immediately, if abnormal liver

function tests persist or worsen, if clinical signs consistent with hepatic disease are established, or if other manifestations occur (e.g. eosinophilia, rash). Hepatitis may occur during use of diclofenac without prodromal symptoms.
Caution is indicated with the use of FLOTAC® in patients with hepatic porphyria, since it may trigger an attack.

Renal effects
As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac, particular caution is required in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or other medicinal products that can significantly impact renal function, and in patients with substantial extracellular volume depletion (e.g. before or after major surgery (see section 4.3)). Monitoring of renal function is recommended as a precautionary measure in such patients. After discontinuation of therapy, patients are normally restored to their pre-treatment state.

Haematological effects
During prolonged treatment with non-steroid anti-inflammatory drugs, including FLOTAC®, monitoring of the blood count is recommended. During therapy with FLOTAC®, as is the case with other NSAIDs, a temporary inhibition of platelet aggregation may occur. Patients with defects of haemostasis should be carefully monitored.

Further information
FLOTAC® should only be used after strict assessment of the risk-benefit ratio in cases of:
- Congenital disorders of porphyrin metabolism (e.g. acute intermittent porphyria);
- Systemic lupus erythematosus (SLE) and mixed connective tissue disease (see section 4.8).

Particularly careful medical supervision is required:
- If renal function is impaired;
- In hepatic dysfunction;
- Immediately after major surgical procedures (warning: increased haemorrhagic diathesis and/or exacerbation of renal function);
- In patients who are allergic to other substances, as they are also at increased risk of experiencing hypersensitivity reactions during use of FLOTAC®.

Respiratory tract diseases
Patients with asthma, hay fever, swollen nasal mucosa (e.g. nasal polyps), chronic obstructive airway diseases or chronic infections of the respiratory tract (especially in conjunction with symptoms such as those that occur in allergic rhinitis) are at increased risk of experiencing allergic reactions. These may manifest as asthma attacks (known as analgesic-induced asthma), angioedema or urticaria. It is therefore recommended that special precautions be taken for such patients (emergency response available). This is also relevant for patients who have an allergic reaction to other substances, e.g. skin reactions, pruritus or urticaria.

Hypersensititvity reactions
Very rarely, severe acute hypersensitivity reactions (e.g. anaphylactic shock) are observed when diclofenac is used. These reactions may occur even without prior exposure to this medicinal product. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac. Therapy must be discontinued at the first signs of a hypersensitivity reaction after taking FLOTAC®. The requisite medical measures appropriate to the symptoms must be initiated by specialist personnel.

As with other NSAIDs, diclofenac may mask the signs and symptoms of an infection due to its pharmacodynamic properties.
The patient is therefore recommended to consult a doctor immediately if signs of a new or worsening infection occur during use of FLOTAC®. It should be assessed whether there is an indication for anti-infective/antibiotic therapy.

Regular monitoring of renal function is required during prolonged administration of FLOTAC®.

Headaches, which must not be treated with increased doses of the medicinal product, may occur with prolonged use of analgesics.

Generally, the habitual use of analgesics, especially when several analgesic substances are combined, can lead to permanent kidney damage with the risk of renal failure (analgesic nephropathy).

When using NSAIDs, including diclofenac, concomitant consumption of alcohol may enhance undesirable effects caused by the active substance, especially those affecting the gastrointestinal tract or central nervous system.

With regard to female fertility, see section 4.6.

4.5 Interaction with other medicinal products and other forms of interaction

Other NSAIDs including salicylates
Concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. Concomitant use of diclofenac with other NSAIDs is therefore not recommended (see section 4.4).

Digoxin, phenytoin, lithium
Concomitant use of FLOTAC® and digoxin, phenytoin or lithium may increase the concentration of these medicinal products in the blood. Monitoring of serum lithium levels is necessary. Monitoring of serum digoxin and serum phenytoin levels is recommended.

Diuretics, ACE inhibitors and angiotensin-II antagonists
NSAIDs can attenuate the effect of diuretics and antihypertensives. In patients with impaired renal function (e.g. dehydrated patients or elderly patients with impaired renal function), concomitant intake of an ACE inhibitor or angiotensin-II antagonist with a medicinal product that inhibits cyclo-oxygenase can lead to further deterioration in renal function, including possible acute renal failure, which is usually reversible. Therefore, such a combination should only be used with caution, especially in elderly patients, whose blood pressure should be regularly monitored. Patients must be instructed to maintain adequate fluid intake and regular monitoring of renal parameters should be considered after the start of combination therapy.

Medicinal products known to trigger hyperkalaemia
Concomitant administration of FLOTAC® and potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may lead to hyperkalaemia. Blood potassium levels should therefore be frequently monitored (see section 4.4).

Glucocorticoids
Increased risk of adverse gastrointestinal effects, e.g. gastrointestinal ulcers or bleeding (see section 4.4).

Methotrexate
Administration of FLOTAC® within 24 hours before or after administration of methotrexate may lead to an elevated concentration of methotrexate in the blood and an increase in its toxic effect.

Ciclosporin and tacrolimus
NSAIDs (such as diclofenac sodium) may increase the nephrotoxicity of ciclosporin and tacrolimus. NSAIDs should therefore be administered at lower doses during concomitant use of ciclosporin or tacrolimus.

Anticoagulants, antiplatelet substances such as acetylsalicylic acid and selective serotonin-reuptake inhibitors (SSRI)
Caution is called for, because concomitant administration may increase the risk of bleeding. Clinical studies do not appear to indicate, however, that diclofenac influences the effect of anticoagulants, but there are reports of an increased risk of bleeding in patients who are given diclofenac and anticoagulants simultaneously. Close monitoring of these patients is recommended

therefore.

NSAIDs can enhance the effect of anticoagulants such as warfarin (see section 4.4).

Increased risk of gastrointestinal bleeding and gastrointestinal side effects (see section 4.4).

Concomitant administration of acetylsalicylic acid reduces plasma diclofenac levels without diminishing clinical efficacy.

Antidiabetics
In clinical studies, it has been shown that diclofenac can be used together with oral antidiabetics without influencing their clinical effect. There have been isolated reports of an effect on blood glucose level (e.g. hyperglycaemia or hypoglycaemia) following administration of diclofenac, which required a dose adjustment of the antidiabetic medication. Monitoring of blood glucose levels is therefore recommended as a precaution in concomitant therapy.
There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with metformin, especially in patients with pre-existing renal impairment.

Probenecid
Medicinal products containing probenecid can delay the excretion of diclofenac.

CYP2C9 inhibitors
Caution is indicated when co-administering diclofenac and CYP2C9 inhibitors (e.g. voriconazole). As degradation of diclofenac is inhibited, there may be a significant increase in exposure and peak plasma concentrations of diclofenac.

CYP2C9 inducers
Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac.

Quinolone antibiotics
There have been isolated reports of cerebral seizures, which may have been attributable to the concomitant use of quinolones and NSAIDs.

Colestipol and colestyramine
These active substances may lead to a delay or decrease in diclofenac absorption. Therefore, it is recommended that diclofenac be used at least 1 hour before or 4 to 6 hours after administration of colestipol/colestyramine.

4.6 Pregnancy and lactation

Pregnancy
The inhibition of prostaglandin synthesis may have an adverse effect on the pregnancy and/or on embryofoetal development. Data from epidemiological studies indicate an increased risk of miscarriage, as well as cardiac malformations and gastroschisis, following the use of a prostaglandin synthesis inhibitor, including diclofenac, in early pregnancy. It is assumed that the risk increases with the dose and duration of therapy.

In animals, it has been shown that the administration of a prostaglandin synthesis inhibitor, including diclofenac, leads to increased pre- and post-implantation loss and to embryofoetal mortality. Furthermore, there have been reports of an increased incidence of various malformations, including cardiovascular malformations, in animals given a prostaglandin synthesis inhibitor, including diclofenac, during the organogenesis phase.

From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment

cessation. Therefore, during the first and second trimester of pregnancy, diclofenac should not be given unless it is absolutely necessary. If diclofenac is used by a woman attempting to conceive, or if it is used during the first and second trimester of pregnancy, the dose should be kept as low as possible and the duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to diclofenac for several days from gestational week 20 onward. diclofenac should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors, including diclofenac:

– May expose the foetus to the following risks:
- Cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, which may progress to renal failure with oligohydramnios (see above);

– May expose the mother and child at the end of pregnancy to the following risks:
- Possible prolongation of bleeding time, a platelet aggregation inhibitory effect which may occur even with very low doses;
- Inhibition of uterine contractions, with the consequence of delayed or prolonged parturition.

Diclofenac is therefore contraindicated during the third trimester of pregnancy.

Breastfeeding
Small quantities of the active substance diclofenac and its metabolites are excreted in human milk. As no adverse consequences for the infant have been reported to date, it will not generally be necessary to interrupt breast-feeding during short-term use. However, if prolonged use or intake of higher doses is prescribed for the treatment of rheumatic diseases, early weaning should be considered.

Fertility
The use of FLOTAC® can, like the use of other medicinal products known to inhibit cyclooxygenase/prostaglandin synthesis, impair female fertility and is therefore not recommended in women wishing to conceive. Discontinuation of FLOTAC® should be considered in women with difficulties in conceiving or who are undergoing investigations for infertility.

4.7 Effects on ability to drive and use machines

Because central nervous side effects, such as tiredness, impaired vision and dizziness, may occur when using FLOTAC®, especially at high dosage, the ability to react, to drive and to use machines may be impaired in individual cases. This applies particularly in combination with alcohol.

4.8 Undesirable effects

The following frequencies are used when assessing undesirable effects:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100) Rare
(≥1/10,000 to <1/1,000) Very rare
(<1/10,000)
Not known (cannot be estimated from the available data)
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following adverse drug reactions include those that have been reported with FLOTAC® and/or other pharmaceutical forms of diclofenac, in both short-term and long-term use.

It is important to remember in relation to the following adverse drug reactions that they are predominantly dose-dependent and that interindividual differences may occur.

The most commonly observed undesirable effects relate to the digestive tract. Peptic ulcers, perforation or bleeding, sometimes fatal, can occur, especially in elderly patients (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, digestive disturbances, abdominal pain, melaena, haematemesis, ulcerative stomatitis and worsening of ulcerative colitis and Crohn's disease (see section 4.4) have been reported following use. Gastritis has been observed less frequently.

Oedema, high blood pressure and heart failure have been reported in connection with NSAID treatment, including diclofenac.

Clinical studies and epidemiological data consistently indicate that the use of diclofenac is associated with increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke) particularly at a high dose (150 mg daily) and in long-term treatment (see section 4.3 and 4.4).

Cardiac disorders
Uncommon*: myocardial infarction, heart failure, palpitations and chest pains
Very rare: oedema
Frequency not known: Kounis syndrome

* Frequency is based on data on long-term treatment with high dosage (150 mg/day).

Blood and lymphatic system disorders
Very rare: haematopoietic disorders (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis), haemolytic anaemia, aplastic anaemia

First signs may be: fever, sore throat, superficial mouth sores, influenza-like symptoms, severe fatigue, nosebleeds and skin bleeding.

The blood count should be regularly monitored in long-term therapy.

Nervous system disorders
Common: central nervous disorders such as headache, dizziness, drowsiness, agitation, irritability or tiredness
Very rare: paraesthesia, dysgeusia, memory impairment, disorientation, seizures, tremor, stroke

Eye disorders
Very rare: disturbed vision (blurred and double vision)

Ear and labyrinth disorders
Common: dizziness
Very rare: tinnitus, temporary hearing disturbances

Gastrointestinal disorders
Very common: gastrointestinal symptoms such as nausea, vomiting and diarrhoea, as well as minor gastrointestinal blood loss which may cause anaemia in exceptional cases Common: dyspepsia, flatulence, abdominal pain, abdominal cramps, loss of appetite, as well as gastrointestinal ulcers (in some circumstances with bleeding, gastrointestinal stenosis, and perforation, which may lead to peritonitis)
Uncommon: haematemesis, melaena or bloody diarrhoea
Rare: gastritis
Very rare: stomatitis (including ulcerative stomatitis), glossitis, oesophageal lesions, lower abdominal complaints (e.g. colitis, haemorrhagic colitis, ischemic colitis, or exacerbation of ulcerative colitis or Crohn’s disease), constipation, pancreatitis and diaphragm-like intestinal strictures
Not known: ischaemic colitis

The patient must be advised to discontinue the medicinal product if significant pain occurs in the upper abdomen, or in the event of melaena or haematemesis, and to consult a doctor immediately.

Renal and urinary disorders
Uncommon: development of oedema, especially in patients with arterial hypertension or renal insufficiency
Very rare: acute kidney injury (acute renal failure), renal tissue damage (interstitial nephritis, papillary necrosis) which may be accompanied by acute renal insufficiency, proteinuria and/or haematuria. Nephrotic syndrome.

Renal function should therefore be checked regularly.

Skin and subcutaneous tissue disorders
Common: inflammatory skin changes
Uncommon: alopecia
Very rare: exanthema, eczema, erythema, photosensitisation, purpura (including allergic purpura) and bullous skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, erythroderma

Infections and infestations
Very rarely, infection-related inflammation (e.g. development of necrotising fasciitis) has been reported to deteriorate in temporal association with the systemic use of NSAIDs. This may be linked to the mechanism of action of NSAIDs.

The patient is therefore recommended to consult a doctor immediately if signs of a new or worsening infection occur during use of FLOTAC®. It should be assessed whether there is an indication for anti-infective/antibiotic therapy. The symptoms of aseptic meningitis with stiff neck, headache, nausea, vomiting, fever or clouded consciousness have been observed in very rare cases during diclofenac use. Patients with auto-immune diseases (SLE, mixed connective tissue disease) appear to be predisposed.

Vascular disorders
Very rare: hypertension, vasculitis

Immune system disorders
Common: hypersensitivity reactions such as rashes and pruritus
Uncommon: urticaria

The patient must be advised in this event to inform the doctor immediately and to stop taking FLOTAC®.
Rare: anaphylactic and anaphylactoid reactions (including hypotension and shock)
Very rare: severe general hypersensitivity reactions. These may manifest as: angioedema including facial oedema, tongue swelling, laryngeal swelling with constriction of the airways, dyspnoea, tachycardia, hypotension and even life- threatening shock.

If any one of these phenomena appears, which may occur even during initial use, FLOTAC® must be discontinued and immediate medical assistance is required.

Very rare: allergic vasculitis and pneumonitis.

Hepatobiliary disorders
Common: elevated serum transaminases
Uncommon: liver damage, especially in long-term therapy, acute hepatitis with or without jaundice (very rarely with a fulminant course, even without prodromal symptoms)
Very rare: liver cell necrosis, hepatic insufficiency

Liver enzyme values should therefore be checked regularly in long-term therapy.

Psychiatric disorders

Very rare: psychotic reactions, depression, anxiety, nightmares, insomnia

Respiratory, thoracic and mediastinal disorders
Rare: asthma (including dyspnoea)
Very rare: pneumonitis

Description of selected adverse drug reactions:

Arteriothrombotic events
Meta-analysis and pharmacoepidemiological data point towards a small increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment.

Visual effects
Visual disturbances such as visual impairment, blurred vision or diplopia appear to be NSAID class effects and are usually reversible on discontinuation. A likely mechanism for the visual disturbances is the inhibition of prostaglandin synthesis and other related compounds that alter the regulation of retinal blood flow resulting in potential changes in vision. If such symptoms occur during diclofenac treatment, an ophthalmological examination may be considered to exclude other causes.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions via the e-mail: drugsafety.cis@novartis.com

4.9 Overdose

a) Symptoms of overdose
Symptoms of overdose may include central nervous disorders such as headaches, dizziness, drowsiness, tinnitus, seizures, hyperventilation, clouded consciousness and loss of consciousness (and also myoclonic seizures in children), as well as abdominal pain, nausea, vomiting and diarrhoea. In addition, gastrointestinal bleeding and hepatic and renal dysfunction are possible. Hypotension, respiratory depression and cyanosis may also occur. In cases of significant intoxication, acute renal failure and liver damage are possible.

b) Therapeutic measures in case of overdose
Treatment of acute intoxication with NSAIDs, including diclofenac, basically consists of supportive measures and symptomatic treatment. There is no specific antidote. Treatment of complications, such as hypotension, renal insufficiency, seizures, gastrointestinal irritation and respiratory depression, is supportive and likewise symptomatic.

Specific measures such as forced diuresis, dialysis or haemoperfusion are not likely to be of benefit in eliminating NSAIDs, including diclofenac, due to their high protein binding and extensive metabolism.

In the event of a potentially toxic overdose, treatment with activated charcoal can be considered. In cases of a potentially life-threatening overdose, gastric decontamination (e.g. gastric lavage) should be carried out.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Anti-inflammatory and antirheumatic products, non-steroids;
Acetic acid derivates and related substances

ATC code: M01AB05

Diclofenac is a non-steroidal anti-inflammatory/antirheumatic agent which, in the usual animal models of inflammation, has been proven to be effective via prostaglandin synthesis inhibition. In humans, diclofenac reduces inflammation-induced pain, swelling and fever. Furthermore, diclofenac inhibits ADP- and collagen-induced platelet aggregation.

5.2 Pharmacokinetic properties

Absorption
The specific pharmaceutical formulation of FLOTAC® ensures that diclofenac release from the colestyramine is both rapid in onset and also persists over a prolonged period.

Following the ingestion of a FLOTAC® hard capsule, measurable diclofenac concentrations are reached in the plasma after just 20 minutes (average: 0.3 micrograms/mL [0.96 micromol/L]). Peak plasma concentrations (C_{max}) after an average of 1.25 hours (scatter: 0.33 to 2 hours) are 0.7 ± 0.22 micrograms/mL (2.2 ± 0.7 micromol/L) and amount to approximately 1/3 of the concentrations found after equivalent doses of Voltaren coated tablets.

Plasma concentrations remain clearly measurable up to 12 hours after administration of FLOTAC®.

In comparison with Voltaren coated tablets in an equivalent dosage, FLOTAC® exhibits more rapid build-up of the active substance, lower peak plasma concentrations, plasma concentrations that are measurable for longer, and lower interindividual variability of peak plasma concentration and of the area under the plasma concentration/time curve.

Linearity/non-linearity
C_{max} values and the areas under the plasma concentration/time curves (AUC values) are linearly proportional to the dose administered.

Distribution
99.7% of the diclofenac is bound to serum proteins, mainly to albumin (99.4%). The volume of distribution is 0.12 to 0.17 L/kg.
Diclofenac passes into the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been reached. The elimination half-life from synovial fluid is 3 to 6 hours.
Only two hours after reaching the peak plasma concentration, the active substance concentration in synovial fluid is higher than in the plasma and remains higher for up to 12 hours.
Diclofenac has been detected at a low concentration (100 ng/mL) in the breast milk of a lactating woman. The calculated amount absorbed by an infant during breast-feeding is equivalent to a daily dose of 0.03 mg/kg body weight.

Biotransformation
The biotransformation of diclofenac is rapid and almost complete.
The metabolites are known. Diclofenac is partly biotransformed by glucuronidation of the unchanged active substance, but mainly by single and multiple hydroxylation which results in the formation of several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5- dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), which are then largely conjugated with glucuronic acid. Two of these phenolic metabolites are pharmacologically active, but significantly less so than diclofenac.

Elimination
Diclofenac is eliminated from the plasma with a systemic clearance of 263 + 56 mL/min. The terminal half-life is 1 to 2 hours.
Four of the metabolites, including the two active metabolites, also have a short half-life of 1 to 3 hours. The practically inactive metabolite 3'-hydroxy-4'-methoxy-diclofenac has a significantly longer half-life.
Less than 1% of the active substance is eliminated renally in unchanged form. Approx.

60% of the quantity administered is excreted as metabolites in the urine and the remainder is excreted via the bile in the faeces.
The pharmacokinetics of diclofenac remain unchanged even after repeated administration.

No accumulation occurs if the recommended dosage intervals are observed.
No significant differences in absorption, metabolism and excretion due to the patient's age have been observed.

Studies following a single IV dose of diclofenac indicate that no accumulation of the unchanged active substance is to be expected in cases of impaired renal function. On the other hand, the studies mentioned suggest that an increase in the concentration of metabolites occurs in the plasma following multiple doses of diclofenac in cases of severely impaired renal function, but without this having clinically detectable repercussions according to current knowledge.

In cases of impaired hepatic function (chronic hepatitis, cirrhosis of the liver without portal decompensation), the kinetics and metabolism proceed as in patients with a healthy liver.

5.3 Preclinical safety data

Apart from the hazards already described in other sections of the prescribing information, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential. The chronic toxicity of diclofenac was evident in animal trials, mainly in the form of lesions and ulcers in the gastrointestinal tract. In a 2-year toxicity study, a dose-dependent increase in thrombotic vascular occlusions was observed in the heart of rats treated with diclofenac.

In animal studies investigating reproductive toxicity, diclofenac led to inhibition of ovulation in rabbits, as well as disturbances of implantation and early embryonic development in rats. The gestation period and duration of parturition were prolonged by diclofenac. The embryotoxic potential of diclofenac was investigated in three animal species (rats, mice, rabbits). Foetal death and growth retardation occurred with doses in the maternally toxic range. On the basis of the available data, diclofenac is not regarded as teratogenic. Doses below the maternally toxic limit had no effect on the postnatal development of the offspring.

6. Pharmaceutical particulars

6.1 List of excipients

Basic cation-exchange resin, titanium dioxide (E171), iron oxide yellow (E172), gelatine, medicinal charcoal, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life is 3 years.

Do not use this medicinal product after the expiry date.

6.4 Special precautions for storage

Do not store above +30°C.
Keep out of the sight and reach of children.

6.5 Nature and contents of container

Nature of container
Blister

20 hard capsules

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Novartis Pharma AG
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4056 Basel,
Switzerland