NOVARTIS

Flotac®

Anti-inflammatory and anti-rheumatic product, non-steroid, acetic acid derivative.

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)
Hard gelatine capsules.

Active substance(s)
The active substance is diclofenac-cholestyramine or [o[(2,6-dichlorophenyl)-amino]-phenyl]-acetate resinate (= diclofenac resinate).

Diclofenac is bound on resinate as an ion exchanger. Resinate is a basic ion exchanger consisting of polymers of styrol and approx. 2% divinylbenzene with groups of quaternary ammonium included in the net structure.

One capsule contains 145.6 mg diclofenac resinate (corresponding to 75 mg diclofenac sodium).

Active moiety
Diclofenac

Excipients
Capsule content: Charcoal activated; weak cationic exchange resin (Cross linked polyacrylic acid resin); magnesium stearate.

Capsule shell content: gelatine; titanium dioxide (E171); iron oxide yellow (E172) and printing ink.

Printing ink: Shellac (E904); propylene glycol; ammonia solution, concentrated; potassium hydroxide; iron oxide black (E172).

INDICATIONS

Treatment of:

- Acute arthritis (including acute attacks of gout).
- Chronic arthritis, especially rheumatoid arthritis (chronic polyarthritis).
- Ankylosing spondylitis (Morbus Bechterew) and other inflammatory, rheumatoid syndroms of the vertrebral column.
- Irritation in degenerative diseases of the joints or the vertebral column (active arthritis and spondylarthritis, cervical syndrom, lumbalgia, ischialgia).
- Inflammatory rheumatism of soft tissues.
- Painful post-traumatic or post-operative swelling and inflammation.
- Painful menstruation (dysmenorrhea without organic findings).
- Pain due to acute or subacute adnexitis (in general an antibiotic treatment is indicated as basic therapy).
- Pain caused by tumor, especially if the skeleton is affected or for inflammatory peritumoral edema.

DOSAGE AND ADMINISTRATION

As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section WARNINGS AND PRECAUTIONS).

General target population
The recommended dose range for Flotac in adults is 1 to maximal 2 capsules per day, depending on the severity of the disorder.

If necessary, adults receive 2 x 1 capsule Flotac per day. The daily dose should be divided into 2 separate doses.

In milder cases, as well as for long-term therapy, 1 capsule per day is usually sufficient.

Special populations
Pediatrics
Because of their dosage strength and the lack of possibility of individual dosing, Flotac capsules are not suitable for children and adolescents.

Geriatrics (Patients aged 65 or above)
No adjustment of the starting dose is required for elderly patients (see section WARNINGS AND PRECAUTIONS).

Established cardiovascular disease or significant cardiovascular risk factors
Treatment with Flotac is generally not recommended in patients with established cardiovascular disease or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease should be treated with Flotac only after careful consideration and only at doses ≤100 mg daily if treated for more than 4 weeks (see section WARNINGS AND PRECAUTIONS).

Renal impairment
Flotac is contraindicated in patients with renal failure (see section CONTRAINDICATIONS).

No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Flotac to patients with mild to moderate renal impairment (see section WARNINGS AND PRECAUTIONS).

Hepatic impairment
Flotac is contraindicated in patients with hepatic failure (see section CONTRAINDICATIONS).

No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Voltaren Resinate to patients with mild to moderate hepatic impairment (see section WARNINGS AND PRECAUTIONS).

Method of administration
The capsules should be swallowed whole with liquid, preferably during meals, and must not be divided or chewed.

CONTRAINDICATIONS

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation (see sections WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS).
- Last trimester of pregnancy (see section WOCBP, PREGNANCY, BREAST-FEEDING AND FERTILITY).
- Hepatic failure.
- Renal failure.
- Severe cardiac failure (see section WARNINGS AND PRECAUTIONS).
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Flotac is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs (see sections WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS).

WARNINGS AND PRECAUTIONS

Gastrointestinal effects
Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs, including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Flotac, the medicinal product should be withdrawn.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercized when prescribing Flotac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section ADVERSE DRUG REACTIONS). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation and in the elderly.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA) or other medicinal products likely to increase 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, anti-platelet agents or selective serotonin-reuptake inhibitors (see section INTERACTIONS).

Close medical surveillance and caution should also be exercized in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section ADVERSE DRUG REACTIONS).

Cardiovascular effects
Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, may be associated with a small increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke).

Treatment with Flotac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking) should be treated with Flotac only after careful consideration and only at doses ≤100 mg daily when treatment continues for more than 4 weeks.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

Hematologic effects
During prolonged treatment with Flotac, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, Flotac may temporarily inhibit platelet aggregation. Patients with defects of hemostasis should be carefully monitored.

Respiratory effects (pre-existing asthma)
In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics/analgesics-asthma), Quincke's edema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Hepatobiliary effects
Close medical surveillance is required when prescribing Flotac to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Flotac, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash) Flotac should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using Flotac in patients with hepatic porphyria, since it may trigger an attack.

Skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including Flotac (see section ADVERSE DRUG REACTIONS). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Flotac should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.

Renal effects
As fluid retention and edema have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section CONTRAINDICATIONS). Monitoring of renal function is recommended as a precautionary measure when using Flotac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Geriatric patients
Caution is indicated in the elderly on basic medical grounds. In particular it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Interaction with other NSAIDs
The concomitant use of Flotac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the potential for additive undesirable effects (see section INTERACTIONS).

Masking signs of infections
Like other NSAIDs, Flotac may mask the signs and symptoms of infection due to its pharmacodynamic properties.

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions
Adverse drug reactions from clinical trials and/or spontaneous or literature reports (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

The following undesirable effects include those reported with Flotac capsules and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Table 1 Adverse drug reactions

Blood and lymphatic system disorders		
	Very rare:	Thrombocytopenia, leukopenia, anemia (including hemolytic and aplastic anemia), agranulocytosis.
Immune system disorders		
	Rare:	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
	Very rare:	Angioedema (including face edema).
Psychiatric disorders		
	Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders		
	Common:	Headache, dizziness.
	Rare:	Somnolence.
	Very rare:	Paresthesia, memory impairment, convulsion, anxiety, tremor, meningitis aseptic, dysgeusia, cerebrovascular accident.
Eye disorders		
	Very rare:	Visual impairment, vision blurred, diplopia.
Ear and labyrinth disorders		
	Common:	Vertigo.
	Very rare:	Tinnitus, hearing impaired.
Cardiac disorders		
	Uncommon*:	Myocardial infarction, cardiac failure, palpitations, chest pain
Vascular disorders		
	Very rare:	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders		
	Rare:	Asthma (including dyspnea).
	Very rare:	Pneumonitis.
Gastrointestinal disorders		
	Common:	Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, decreased appetite.
	Rare:	Gastritis, gastrointestinal hemorrhage, hematemesis, diarrhea hemorrhagic, melena, gastrointestinal ulcer (with or without bleeding or perforation).
	Very rare:	Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, esophageal disorder, intestinal diaphragm disease, pancreatitis.
Hepatobiliary disorders		
	Common:	Transaminases increased.
	Rare:	Hepatitis, jaundice, liver disorder.
	Very rare:	Hepatitis fulminant, hepatic necrosis, hepatic failure
Skin and subcutaneous tissue disorders		
	Common:	Rash.
	Rare:	Urticaria.
	Very rare:	Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus.
Renal and urinary disorders		
	Very rare:	Renal failure acute, hematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions		
	Rare:	Edema.

* The frequency reflects data from long-term treatment with a high dose (150 mg daily).

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 (see section WARNINGS AND PRECAUTIONS).

INTERACTIONS

The following interactions include those observed with Flotac capsules and/or other pharmaceutical forms of diclofenac.

Observed interactions to be considered
Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

***Lithium*:** If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

***Diuretics and antihypertensive agents*:** Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity (see section WARNINGS AND PRECAUTIONS).

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

***Drugs known to cause hyperkalemia*:** Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section WARNINGS AND PRECAUTIONS).

Quinolone antibacterials: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

Due to the fact that resinate is a basic ion exchanger, generally an inhibition of absorption of other orally given medicinal products has to be taken into account.

Anticipated interactions to be considered
***Other NSAIDs and corticosteroids*:** Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section WARNINGS AND PRECAUTIONS). Concomitant administration of acetylsalicylic acid decreases the plasma concentration of diclofenac, without compromising clinical efficacy.

***Anticoagulants and anti-platelet agents*:** Caution is recommended since concomitant administration could increase the risk of bleeding (see section WARNINGS AND PRECAUTIONS). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated reports of an increased risk of hemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see section WARNINGS AND PRECAUTIONS).

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycemic and hyperglycemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

***Methotrexate*:** Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

Women of child-bearing potential
There are no data to suggest any recommendations for women of child-bearing potential.

Pregnancy
There are insufficient data on the use of diclofenac in pregnant women. Therefore, Flotac should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus (see sections CONTRAINDICATIONS and NON-CLINICAL SAFETY DATA).

Breast-feeding
Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, Flotac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

Fertility
As with other NSAIDs, the use of Flotac may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Flotac should be considered.

OVERDOSAGE

Symptoms
There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal hemorrhage, diarrhea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures
Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or hemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life-threatening overdose.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)
Diclofenac, the active substance of Flotac, is a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain and fever.

Diclofenac *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

Resinate is a basic ion exchanger, on which diclofenac is bound as anion. The resinate part of Flotac is not absorbed from the gastrointestinal tract and is eliminated via the faeces. The dosage of resinate per capsule Flotac is approx. 100 to 200 times lower than the dosage recommended for therapy of various forms of lipodystrophia.

Pharmacodynamics (PD)
In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterized by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

In post-traumatic and post-operative inflammatory conditions, diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound edema.

In addition, the active substance is capable of relieving the pain and reducing the extent of bleeding in primary dysmenorrhea.

Pharmacokinetics (PK)
Absorption
The special galenic properties of Flotac result in a quick onset as well as in a long-lasting release of diclofenac from the resinate.

After single administration of a Flotac capsule, diclofenac concentrations can be measured in the plasma (mean 0.3 micrograms/mL [0.96 micromol/L]) after 20 minutes. Peak plasma concentrations (C_{max}) of 0.7 ± 0.22 micrograms/mL (2.2 ± 0.7 micromol/L) are attained within 1.25 hours (SD 0.33 to 2 hours) and are about one third of those achieved following administration of Voltaren Dragées (gastro-resistant tablets).

Plasma levels can be measured up to 12 hours after administration of Flotac.

In comparison with the equivalent dosage of Voltaren gastro-resistant tablets, Flotac shows a quicker absorption of the active substance, lower peak plasma concentrations, longer measurable plasma level as well as lower interindividual differences of the peak plasma concentrations and the area under the concentration curve.

Comparison of the plasma concentrations after i.v. resp oral administration of radioactive marked diclofenac show that also after oral administration the whole dose of the substance is available systemically. Out of this up to approx. 54% consist of unchanged active substance, the rest consists of partially active metabolites (first-pass-metabolism) (see section CLINICAL PHARMACOLOGY subsection Pharmacodynamics (PD)).

In comparison with Voltaren 50 gastro-resistant tablets the bioavailability of diclofenac from Flotac capsules reaches a mean value of 78 ± 18% (SD: 62 to 117%).

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distribution
99.7% diclofenac is bound to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 L/kg.

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours.

Two hours after reaching peak plasma values, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

Biotransformation/metabolism
Biotransformation of diclofenac is quick and almost complete. The metabolites are known. Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac.

Elimination
Total systemic clearance of diclofenac from plasma is 263 ±56 mL/min (mean value ± SD).

The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive.

About 60% of the dose absorbed is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Linearity/non-linearity
C_{max} as well as the area under the concentration curve (AUC) are linearly related to the size of the administered dose.

Special populations
No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed.

Trials in patients suffering from renal impairment show that an accumulation of the unchanged active substance following a single-dose i.v. administration is unlikely. However, based on the results from these studies, elevated plasma levels of the hydroxy metabolites after multiple dose may be expected in patients suffering from severe renal impairment. According to the actual status of knowledge, this is not clinically relevant.

In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

CLINICAL STUDIES

Flotac is a well established product.

NON-CLINICAL SAFETY DATA

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. In standard preclinical animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac had no influence on the fertility of parent animals in rats. Except for minimal fetal effects at maternally toxic doses, the prenatal, perinatal and postnatal development of the offspring was not affected.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors (see sections CONTRAINDICATIONS and WOCBP, PREGNANCY, BREAST-FEEDING AND FERTILITY).

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Store in the original package in order to protect from moisture.

Flotac capsules should not be used after the date marked "EXP" on the pack.

Flotac capsules must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

Manufacturer:
See folding box.

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