NOVARTIS

CATAFLAM®

(diclofenac potassium)

Sugar-coated tablet

Product Information

Based on CDS version 3.0 (08-Sep-2022)

Cardiovascular risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This may increase with dose and duration of use. Cataflam is contraindicated in established congestive heart failure (New York Heart Association [NYHA] classification II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. Patients with congestive heart failure (NYHA-I) or risk factors for cardiovascular disease may be at greater risk (see section 6 Warnings and precautions).
- Cataflam is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see section 6 Warnings and precautions).

Gastrointestinal risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see section 6 Warnings and precautions).

1 Trade name(s)

CATAFLAM® (25 mg sugar-coated tablets)

CATAFLAM® (50 mg sugar-coated tablets)

2 Description and composition

Pharmaceutical form(s)

Sugar-coated tablets

25 mg

Round, biconvex, sugar-coated tablet pale-red, shiny, and practically odorless.

50 mg

Round tablet, biconvex, reddish brown sugar-coated tablets and practically odorless.

Active substance(s)

The active ingredient is diclofenac potassium. One Cataflam tablet contains 25 mg or 50 mg of diclofenac potassium. In Cataflam the sodium ion of diclofenac sodium (Voltaren) has been replaced by a potassium ion. The active principle is thus the same as in Voltaren.

Excipients

Core: magnesium stearate, polyvinylpyrrolidone, silicon dioxide, sodium carboxymethyl starch (sodium starch glycolate), maize (corn) starch, calcium phosphate, purified water.

Coat: microcrystalline cellulose, polyethylene glycol 8000, dispersed red, polyvinylpyrrolidone, talc, sucrose, purified water.

Polish: polyethylene glycol 8000, sucrose, ethanol, purified water.

3 Indications

- For the acute and chronic treatment of signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.
- For the management of pain and primary dysmenorrhea, when prompt pain relief is desired.
- Short-term treatment in the acute migraine attacks.
- Short-term treatment in the post-operative pain and inflammation following dental and orthopedic surgery.

4 Dosage regimen and administration

Dosage regimen

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 6 Warnings and precautions).

General target population

Adults

The maximum daily dose is 100 mg to be divided in separate doses and used for the shortest possible duration. An initial maximum daily dose of 150 mg can be used on the first day.

The total daily dose should generally be divided into 2 to 3 separate doses, as applicable. In migraine, an initial dose of 50 mg should be taken at the first signs on an impending attack. In cases where pain relief within 2 hours after the first dose is not sufficient, a further dose of 50 mg may be taken. If needed, further doses of 50 mg may be taken at intervals of 4 to 6 hours, not exceeding a total dose of 100 mg per day.

In some conditions the dose may be adjusted based on physician's assessment, after careful consideration following a risk-benefit analysis.

Special populations

Renal impairment

Cataflam is contraindicated in patients with renal failure (GFR <15 mL/min/1.73 m^2) (see section 5 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

Cataflam to patients with mild to moderate renal impairment (see section 6 Warnings and precautions).

Hepatic impairment

Cataflam is contraindicated in patients with hepatic failure (see section 5 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 Cataflam to patients with mild to moderate hepatic impairment (see section 6 Warnings and precautions).

Pediatric patients (below 18 years)

Cataflam tablets are not recommended for use in children.

Geriatric patients (65 years of age or above)

Caution is indicated on basic medical grounds, especially for frail elderly patients or those with a low body weight (see section 6 Warnings and precautions).

Congestive heart failure (NYHA-I) or significant cardiovascular risk factors

Patients with congestive heart failure (NYHA-I) or patients with significant risk factors for cardiovascular disease should be treated with Cataflam only after careful consideration.

Method of administration

The tablets should be swallowed whole with liquid, preferably before meals, and must not be divided or chewed.

5 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Cataflam should not be given to patients who have experienced asthma, urticaria, or allergic type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see section 6 Warnings and precautions – Anaphylactoid Reactions).
- Active gastric or intestinal ulcer, bleeding or perforation (see sections 6 Warnings and precautions and 7 Adverse drug reactions).
- Last trimester of pregnancy (see section 9 Pregnancy, lactation, females and males of reproductive potential).
- Hepatic failure.
- Renal failure (GFR < 15 mL/min/1.73 m^2).
- Established congestive heart failure (New York Heart Association [NYHA] classification II-IV).
- Ischemic heart disease.

- Peripheral arterial disease and/or cerebrovascular disease.
- Cataflam is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see section 6 Warnings and precautions).
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Cataflam is also contraindicated in patients in whom the use of acetylsalicylic acid or other NSAIDs can precipitate asthma, angioedema, urticaria, or acute rhinitis (i.e., NSAID-induced cross-reactivity reactions) (see sections 6 Warnings and precautions and 7 Adverse drug reactions).

6 Warnings and precautions

Cardiovascular effects

- **Cardiovascular thrombotic events**

Clinical trials of several COX-2 selective and non-selective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistence evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see **Gastrointestinal effects**).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following coronary artery bypass graft (CABG) surgery found an increased incidence of myocardial infarction and stroke (see section 5 Contraindications).

- **Hypertension**

NSAIDs, including Cataflam, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including Cataflam, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

- **Edema**

Fluid retention and edema have been observed in some patients taking NSAIDs. Cataflam should be used with cautions in patients with fluid retention.

Congestive heart failure (NYHA-I) or significant cardiovascular risk factor

Patients with congestive heart failure (NYHA-I) or patients with significant risk factors for cardiovascular disease should be treated with Cataflam only after careful consideration.

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.

Gastrointestinal effects

Serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine, 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. Only one in five patients, who develop a serious upper GI adverse events on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. This trends continue with longer duration of use, increasing the likelihood of developing a serious GI events at some time during the course of therapy. However, even short-term therapy is not without risk. If gastrointestinal bleeding or ulceration occurs in patients receiving Cataflam, the treatment should be discontinued.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Cataflam in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 7 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. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious adverse event is suspected. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

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 low dose acetylsalicylic acid (ASA), or other drugs 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 8 Interactions).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may by exacerbated (see section 7 Adverse drug reactions).

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

Hematological effects

Use of Cataflam is recommended only for short-term treatment. If, however, Cataflam is used for a prolonged period, monitoring of the blood count is recommended, as with other NSAIDs. Like other NSAIDs, diclofenac 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 caution 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 Cataflam 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 Cataflam (e.g., in the form of tablets or suppositories), 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), Cataflam should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using Cataflam 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 Cataflam (see section 7 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. Cataflam 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 of any cause, e.g., before or after major surgery (see section 5 Contraindications). Monitoring of renal function is recommended as a precautionary measure when using Cataflam in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Long term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Advance renal disease

No information is available from controlled clinical studies regarding the use of Cataflam in patients with advanced renal disease. Therefore, treatment with Cataflam is not recommended in these patients with advanced renal disease. If Cataflam therapy must be initiated, close monitoring of the patient’s renal function is advisable.

Anaphylactoid reactions

As with other NSAIDs, anaphylactoid reactions may occur with diclofenac in patients without known prior exposure to the drug. Cataflam should not be given to patients with the aspirin trial. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or

without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see section 5 Contraindications). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Geriatric patients

Caution is indicated in the elderly on basic medical grounds especially in frail elderly patients or those with a low body weight.

Interactions with NSAIDs

The concomitant use of Cataflam with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects (see section 8 Interactions).

Masking signs of infections

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

Excipients

Cataflam tablets contain sucrose and therefore are not recommended for patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

Effects on ability to drive or use machines

Patients experiencing visual disturbances, headache, dizziness, vertigo, somnolence or other central nervous system disturbances while taking Cataflam, should refrain from driving or using machines.

7 Adverse drug reactions

Tabulated summary of adverse drug reactions

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 7-1) 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 Cataflam and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Table 7-1 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, aseptic meningitis, dysgeusia, cerebrovascular accident.
Eye disorders	
Very rare:	Visual impairment, blurred vision, diplopia.
Ear and labyrinth disorders	
Common :	Vertigo.
Very rare:	Tinnitus, impaired hearing.
Cardiac disorders	
Uncommon*:	Myocardial infarction, cardiac failure, palpitations, chest pain.
Frequency not known:	Kounis syndrome.
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, epigastric pain.
Rare:	Gastritis, gastrointestinal hemorrhage, hematemesis, hemorrhagic diarrhea, melena, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis, or perforation, which may lead to peritonitis).
Very rare:	Colitis (including hemorrhagic colitis, ischemic 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:	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common:	Rash.
Rare:	Urticaria.

Very rare:	Bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus.
Renal and urinary disorders	
Very rare:	Acute kidney injury (acute renal failure), 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/day).

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 6 Warnings and precautions).

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.

8 Interactions

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

Observed interactions to be considered

CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac.

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 6 Warnings and precautions).

Ciclosporin and tacrolimus: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin and tacrolimus 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 or tacrolimus.

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 6 Warnings and precautions).

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

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 6 Warnings and precautions).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 6 Warnings and precautions). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are 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 6 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 hypoglycaemic and hyperglycaemic 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.

There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with metformin, especially in patients with pre-existing renal impairment.

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.

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.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

There are insufficient data on the use of diclofenac in pregnant women. Some epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy, however the overall data are inconclusive.

Diclofenac has been shown to cross the placental barrier in humans. Use of NSAIDs, including diclofenac, can cause uterine inertia, premature closure of the fetal ductus arteriosus and fetal renal impairment leading to oligohydramnios.

Because of these risks, Cataflam should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus.

In addition, Cataflam should not be used during the third trimester of pregnancy (see section 5 Contraindications).

In animal reproduction studies, no evidence of teratogenicity was observed in mice, rats, or rabbits given diclofenac daily during the period of organogenesis at doses up to approximately 0.41, 0.41, and 0.81 times, respectively, the maximum recommended human dose (MRHD) of Cataflam, despite the presence of maternal and fetal toxicity (see Animal data).

Clinical considerations

Fetal Adverse Drug Reactions

Premature Closure of Fetal Ductus Arteriosus

As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of premature closure of the fetal ductus arteriosus (see section 5 Contraindications).

Oligohydramnios/Fetal Renal Impairment

Risk of fetal renal impairment with subsequent oligohydramnios has been observed when NSAIDs (including diclofenac) were used from the 20th week of pregnancy onwards.

If an NSAID is necessary from the 20th week gestation to the end of the 2nd trimester, limit the use to the lowest effective dose and shortest duration possible (see section 4 Dosage regimen and administration). If Cataflam treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue Cataflam and follow up according to clinical practice.

Labor or Delivery

There are no studies on the effects of Cataflam during labor or delivery. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia (see section 5 Contraindications). In animal studies, NSAIDS, including diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus

Published literature reports that the use of NSAIDs during the third trimester of pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Fetal Renal Impairment

Published studies and post-marketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal impairment leading to oligohydramnios. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug.

Animal Data

Reproductive and developmental studies in animals demonstrated that diclofenac administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day (0.41 times the maximum recommended human dose [MRHD] of Cataflam, 200 mg/day, based on body surface area (BSA) comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (0.41 and 0.81 times, respectively, the MRHD based on BSA comparison).

In a study in which pregnant rats were orally administered 2 or 4 mg/kg diclofenac (0.08 and 0.16 times the MRHD based on BSA) from Gestation Day 15 through Lactation Day 21, significant maternal mortality (caused by gastrointestinal ulceration and peritonitis) was noted. These maternally toxic doses were associated with dystocia, prolonged gestation, intrauterine growth retardation, and decreased fetal survival.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the fetal ductus arteriosus.

9.2 Lactation

Risk Summary

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

Human Data

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother treated orally with a diclofenac salt of 150 mg/day. The estimated dose ingested by an infant consuming breast milk is equivalent to 0.03 mg/kg/day.

9.3 Females and males of reproductive potential

Female fertility

As with other NSAIDs, the use of Cataflam 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 Cataflam should be considered.

Male fertility

There is no human data on the effect of Cataflam on male fertility.

Diclofenac administered to male and female rats at 4 mg/kg/day (approximately 0.16 times the MRHD based on BSA comparison) did not affect fertility.

10 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.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances (ATC code: M01AB05).

Mechanism of action (MOA)

Cataflam contains diclofenac potassium, a non-steroidal compound with pronounced antirheumatic, analgesic, anti-inflammatory, and antipyretic properties.

Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain and fever.

Cataflam tablets have a rapid onset of action which makes them particularly suitable for the treatment of acute painful and inflammatory conditions.

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

Pharmacodynamics (PD)

Cataflam has been found to exert a pronounced analgesic effect in moderate and severe pain. In the presence of inflammation, e.g., due to trauma or following surgical interventions, it rapidly relieves both spontaneous pain and pain on movement and diminishes inflammatory swelling and wound oedema.

Clinical studies have also revealed that in primary dysmenorrhoea the active substance is capable of relieving the pain and reducing the extent of bleeding.

In migraine attacks Cataflam has been shown to be effective in relieving the headache and in improving the accompanying symptoms nausea and vomiting.

Pharmacokinetics (PK)

Absorption

Diclofenac is rapidly and completely absorbed from diclofenac potassium tablets. The absorption sets in immediately after administration and the same amount is absorbed as from an equivalent dose of diclofenac sodium enteric coated tablets.

Mean peak plasma concentrations of 3.8 µmol/L are attained after 20-60 minutes after ingestion of one tablet of 50 mg. Ingestion together with food has no influence on the amount of diclofenac absorbed although onset and rate of absorption may be slightly delayed.

Since about half of diclofenac is metabolized during its first passage through the liver (“first pass” effect), the area under the concentration curve (AUC) is about half as large following oral or rectal administration as it is following a parenteral dose of equal size.

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

Distribution

99.7% of 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 reached. 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.

Biotransformation/metabolism

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 lesser 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 administered dose 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 feces.

Linearity/non-linearity

The amount absorbed is in linear proportion to the size of the dose.

Special populations

Geriatric patients

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

Renal impairment

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule.

At a creatinine clearance of less than 10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects.

However, the metabolites are ultimately cleared through the bile.

Hepatic impairment

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

12 Clinical studies

Cataflam is a well-established product.

13 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.

For more information, see section 9 Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

Incompatibilities
Not applicable.

Storage
Do not store above 30°C. Protect from heat and moisture.

Keep out of the reach and sight of children.

Shelf-life
The expiry date is indicated on the packaging.

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Pack size

Cataflam 25 mg sugar-coated tablet Reg. No. DKL9930408316A1
Box, 5 blisters @ 10 sugar-coated tablets

Cataflam 50 mg sugar-coated tablet Reg. No. DKL9930408316B1
Box, 5 blisters @ 10 sugar-coated tablets

Marketing Authorization Holder
PT Novartis Indonesia

Manufacturer

Manufactured by Novartis Saglik Gida Ve Tarim Urunleri Sanayi Ve Ticaret Anonim Sirketi, Kurtkoy, Turkey
For Novartis Pharma AG, Basel, Switzerland

Product Information based on CDS version 3.0 (08-Sep-2022)