

## Regulatory Affairs

**CATAFLAM®** (diclofenac potassium)  
75 mg/3 mL Solution for injection  
25 mg and 50 mg Sugar-coated tablets  
50 mg Soft capsules  
12.5 mg, 25 mg and 75 mg Suppositories

## Prescribing Information

### Version 2.2

**NOTICE** The Novartis Core Data Sheet (CDS) displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.  
The Novartis CDS contains all relevant information relating to indications, dosing, pharmacovigilance and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

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### 1 Trade names

#### Solution for injection (Inj)

CATAFLAM® 75 mg/3 mL solution for injection.

#### Sugar-coated tablets (SCT)

CATAFLAM® 25 mg sugar-coated tablets.

CATAFLAM® 50 mg sugar-coated tablets.

#### Soft capsules (SC)

CATAFLAM® 50 mg soft capsules.

#### Suppositories (Sup)

CATAFLAM® 12.5 mg suppositories.

CATAFLAM® 25 mg suppositories.

CATAFLAM® 75 mg suppositories.

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## 2 Description and composition

### Pharmaceutical forms

Solution for injection.

Sugar-coated tablets.

Soft capsules.

Suppositories.

### Active substance

The active substance is diclofenac potassium. In Cataflam® the sodium ion of diclofenac sodium (Voltaren®) has been replaced by a potassium ion.

#### Solution for injection

One Cataflam ampoule of 3 mL contains 75 mg of diclofenac potassium.

#### SCT

One Cataflam sugar-coated tablet contains 25 mg or 50 mg of diclofenac potassium. **SC**

One Cataflam soft capsule contains 50 mg of diclofenac potassium.

#### Suppositories

One Cataflam suppository contains 12.5 mg, 25 mg or 75 mg of diclofenac potassium.

### Active moiety

Diclofenac

### Excipients

#### Solution for injection

Sodium metabisulphite (E223), disodium edetate dihydrate, mannitol, benzyl alcohol, propylene glycol, potassium hydroxide, water for injection.

#### SCT

**Core:** Magnesium stearate; povidone; silica colloidal anhydrous; sodium starch glycollate; maize starch; calcium phosphate.

**Sugar-coat:** Microcrystalline cellulose; polyethylene glycol 8000; red iron oxide (E172) and titanium dioxide (E171) (dispersed Anstead); povidone; talc; sucrose.

**Polish:** polyethylene glycol 8000; sucrose.

**Imprint** with printing ink brown for 25 mg and white for 50 mg.

#### SC

**Capsule content:** Macrogol 600/polyethylene glycol 600, glycerol 85% and purified water.

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**Capsule shell:** gelatin, glycerol 85%, Polysorb 85/70/00, Quinoline Yellow 70% (E104, CI 47005) and purified water.

**Printing ink, white:** shellac, titanium dioxide, and propylene glycol.

**Suppositories** Hard

fat.

Information might differ in some countries.

### **3 Indications**

Short-term treatment in the following acute conditions:

#### **Solution for injection**

Treatment of:

- Post-traumatic pain, inflammation and swelling, e.g. due to sprains [147,148].
- Post-operative pain, inflammation and swelling, e.g. following dental or orthopedic surgery [20,149-156].
- Renal colic and biliary colic.

#### **SCT and SC**

Treatment of:

- Post-traumatic pain, inflammation and swelling, e.g. due to sprains [148].
- Post-operative pain, inflammation and swelling, e.g. following dental or orthopedic surgery [20,149-156]
- Painful and/or inflammatory conditions in gynecology, e.g. primary dysmenorrhea or adnexitis [157,158].
- Migraine attacks [166,167].
- Painful syndromes of the vertebral column.
- Non-articular rheumatism.
- As an adjuvant in severe painful inflammatory infections of the ear, nose or throat, e.g. pharyngotonsillitis, otitis [159,161-163]. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

#### **Suppositories**

Treatment of:

- Post-traumatic pain, inflammation and swelling, e.g. due to sprains
- Post-operative pain, inflammation and swelling, e.g. following dental or orthopedic surgery
- Painful and/or inflammatory conditions in gynecology, e.g. primary dysmenorrhea or adnexitis
- Painful syndromes of the vertebral column.

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- Non-articular rheumatism.
  - As an adjuvant in severe painful inflammatory infections of the ear, nose or throat, e.g. pharyngotonsillitis, otitis. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

## 4 Dosage and administration

### Dosage

As a general recommendation, the dose should be individually adjusted [168]. 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) [184].

### General target population: adults

#### Solution for injection

Cataflam solution for injection should not be given for more than 2 days; if necessary, treatment can be continued with Cataflam tablets or suppositories (see Method of administration).

#### SCT

The recommended initial daily dose is 100 to 150 mg. In milder cases, 75 to 100 mg daily is usually sufficient.

The total daily dose should generally be divided into 2 or 3 separate doses, as applicable.

In primary dysmenorrhea, the daily dose should be individually adjusted and is generally 50 to 150 mg. An initial dose of 50 mg is usually sufficient. If necessary, an initial dose of 100 mg can be prescribed with a maximum of 200 mg/day reached over the course of several menstrual cycles. Treatment should be started on appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

In migraine, an initial dose of 50 mg should be taken at the first signs of 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 200 mg per day [183].

#### SC

The recommended initial daily dose is 100 to 150 mg. In milder cases, 50 to 100 mg daily may be sufficient. The daily dose should generally be divided into 2 or 3 separate doses, as applicable.

In primary dysmenorrhoea, the daily dose should be individually adjusted and is generally 50 to 150 mg. An initial dose of 50 mg is usually sufficient. If necessary, an initial dose of 100 mg can be prescribed with a maximum of 200 mg/day reached over the course of several menstrual cycles. Treatment should be started on appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

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In migraine, an initial dose of 50 mg should be taken at the first signs of 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 200 mg per day.

### **Suppositories**

The recommended initial daily dose is 100 to 150 mg. In milder cases, 75 to 100 mg daily is usually sufficient. The total daily dose should generally be divided into 2 or 3 separate doses, as applicable.

In primary dysmenorrhea, the daily dose should be individually adjusted and is generally 50 to 150 mg. An initial dose of 50 mg is usually sufficient. If necessary, an initial dose of 100 mg can be prescribed with a maximum of 200 mg/day reached over the course of several menstrual cycles. Treatment should be started on appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

### **Special populations**

#### **Pediatric patients (below 18 years of age)**

#### **Solution for injection**

Because of their dosage strength, the ampoules of Cataflam solution for injection are not suitable for use in children and adolescents [168].

#### **SCT**

Cataflam tablets are not recommended for use in children and adolescents below 14 years of age. For treatment in children and adolescents below 14 years of age, oral drops or suppositories of diclofenac 12.5 mg and 25 mg could be used. For adolescents aged 14 years and over, a daily dose of 75 to 100 mg is usually sufficient. The maximum daily dose of 150 mg should not be exceeded [168]. The total daily dose should generally be divided into 2 to 3 separate doses, as applicable.

The use of Cataflam (all forms) in migraine attacks has not been established in children and adolescents [168].

#### **SC**

Cataflam soft capsules are not recommended for use in children and adolescents below 14 years of age. For treatment in children and adolescents below 14 years of age, oral drops and suppositories of diclofenac 12.5 mg and 25 mg are available.

For adolescents aged 14 years and over, 50 to 100 mg daily may be sufficient. The maximum daily dose of 150 mg should not be exceeded [168]. The daily dose should generally be divided in 2 or 3 separate doses, as applicable.

The use of Cataflam soft capsules in migraine attacks has not been established in children and adolescents. **Suppositories**

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Children aged 1 year or over and adolescents should be given 0.5 to 2 mg/kg body weight daily, depending on the severity of the disorder. For adolescents aged 14 years or over, 75 to 100 mg daily is usually sufficient. The maximum daily dose of 150 mg should not be exceeded. The daily dose should generally be divided into 2 or 3 separate doses, as applicable.

Because of their dosage strength, Cataflam 75 mg suppositories are not suitable for children and adolescents [168].

### **Geriatric patients (aged 65 years or above)**

No adjustment of the starting dose is generally required for elderly patients. However, 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) [180,185].

### **Established cardiovascular disease or significant cardiovascular risk factors**

Treatment with Cataflam 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 Cataflam only after careful consideration and only at doses  $\leq 100$  mg daily if treated for more than 4 weeks (see section 6 Warnings and precautions) [184].

### **Renal impairment**

Cataflam is contraindicated in patients with renal failure (GFR  $< 15$  mL/min/1.73m<sup>2</sup>) (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 renal impairment (see section 6 Warnings and precautions) [184,185].

### **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) [184].

### **Method of administration**

#### **Solution for injection**

The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site (which may result in muscle weakness, muscle paralysis and hypoaesthesia) [185].

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The dose is generally one 75 mg ampoule daily, given by deep intragluteal injection into the upper outer quadrant using aseptic technique [185]. In severe cases (e.g. colic), the daily dose can exceptionally be increased to two injections of 75 mg, separated by an interval of a few hours (one into each buttock). Alternatively, one ampoule of 75 mg can be combined with other pharmaceutical forms of Cataflam (e.g. tablets, suppositories, oral drops) up to a total maximum daily dose of 150 mg.

### **SCT and SC**

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

### **Suppositories**

The suppositories should be inserted well into the rectum. It is recommended to take the suppositories after passing stools.

**Not** to be taken by mouth, as for rectal use only.

## **5 Contraindications**

- Known hypersensitivity to the active substance, sodium metabisulphite (*solution for injection only*) or any of the other excipients.
- Active gastric or intestinal ulcer, bleeding or perforation (see sections 6 Warnings and precautions and 7 Adverse drug reactions) [169].
- Last trimester of pregnancy (see section 9 WOCBP, pregnancy, breast-feeding and fertility) [169].
- Hepatic failure.
- Renal failure (GFR <15 mL/min/1.73m<sup>2</sup>) [185].
- Severe cardiac failure (see section 6 Warnings and precautions) [169].
- 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 crossreactivity reactions) [186] (see sections 6 Warnings and precautions and 7 Adverse drug reactions) [78,79].
- Proctitis (*suppositories only*).

## **6 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 [145]. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Cataflam, the treatment should be discontinued [169].



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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 [169].

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 [169].

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 [169].

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) [169].

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section 7 Adverse drug reactions) [169].

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 [187].

### **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 Cataflam 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 Cataflam only after careful consideration and only at doses  $\leq 100$  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. [184].

### **Hematologic 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 [22,85]. Patients with defects of hemostasis should be carefully monitored [86,87].

### **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 [169].

Special caution is recommended when Cataflam is used parenterally in patients with bronchial asthma because symptoms may be exacerbated (*solution for injection only*).

### **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 NSAID, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Cataflam, 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 [82-84].

### **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 [169].

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

[80], history of hypertension [169], 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 5 Contraindications) [44,169]. 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 [169].

### Geriatric patients

Caution is indicated in the elderly on basic medical grounds, especially in frail elderly patients or those with a low body weight [81,185].

### Interactions with NSAIDs

The concomitant use of Cataflam with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the potential for additive undesirable effects (see section 8 Interactions) [169].

### Special excipients

#### Solution for injection

The sodium metabisulphite in the solution for injection can lead to severe isolated hypersensitivity reactions and bronchospasm.

### Masking signs of infections

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

## 7 Adverse drug reactions

### Tabulated summary of adverse drug reactions

Adverse drug reactions from clinical trials and/or spontaneous or literature reports (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 ( $\geq 1/100$  to  $<1/10$ ); uncommon ( $\geq 1/1,000$  to  $<1/100$ ); rare ( $\geq 1/10,000$  to  $<1/1,000$ ); very rare ( $<1/10,000$ ). The following undesirable effects include those reported with Cataflam solution for injection and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

**Table 7-1** Adverse drug reactions [169,181]

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Infections and infestations (*solution for injection only*)

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Very rare:	Injection site abscess [169].
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<b>Blood and lymphatic system disorders</b>	
Very rare:	Thrombocytopenia, leukopenia, anemia (including hemolytic and aplastic anemia), agranulocytosis [24,125-130].

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<b>Immune system disorders</b>	
Rare:	Hypersensitivity, anaphylactic and anaphylactoid reactions [131] (including hypotension and shock) [169].
Very rare:	Angioedema (including face edema) [169].

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<b>Psychiatric disorders</b>	
Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder [32,34,101,102].

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<b>Nervous system disorders</b>	
Common:	Headache, dizziness [24,32,34].
Rare:	Somnolence [34].
Very rare:	Paresthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis [32,34,101,102], dysgeusia [32,34,139,140], cerebrovascular accident [169].

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<b>Eye disorders</b>	
Very rare:	Visual impairment, blurred vision, diplopia [32,34,139,140].

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<b>Ear and labyrinth disorders</b>	
Common:	Vertigo [24,32,34].
Very rare:	Tinnitus, impaired hearing [32,34,139,140].

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<b>Cardiac disorders</b>	
Uncommon* [184]:	Myocardial infarction [169], cardiac failure [81,136-138], palpitations, chest pain.
Frequency not known	Kounis syndrome [186]

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<b>Vascular disorders</b>	
Very rare:	Hypertension [81,136-138], vasculitis [105,132-135].

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<b>Respiratory, thoracic and mediastinal disorders</b>	
Rare:	Asthma (including dyspnea) [131].
Very rare:	Pneumonitis [105,132-135].

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<b>Gastrointestinal tract disorders</b>	
Common:	Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, decreased appetite [24,89].
Rare:	Gastritis [169], gastrointestinal hemorrhage, hematemesis, hemorrhagic diarrhea, melena, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis, or perforation, which may lead to peritonitis) [24,32,34,89,90,93,96,97,185], proctitis [169] ( <i>suppositories only</i> ).
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 [89-96,98-100,185], hemorrhoids [169] ( <i>suppositories only</i> ).

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<b>Hepatobiliary disorders</b>	
Common:	Transaminases increased [24].
Rare:	Hepatitis, jaundice [120-123], liver disorder [169].
Very rare:	Fulminant hepatitis [124], hepatic necrosis, hepatic failure [176].

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**Skin and subcutaneous tissue disorders**

Common:	Rash [24,32,34].
Rare:	Urticaria [79,103].
Very rare:	Bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schoenlein purpura [104-110], pruritus [169].

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**Renal and urinary disorders**

Very rare:	Acute kidney injury (acute renal failure), hematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis [111,119,185].
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**General disorders and administration site conditions**

Common:	Injection site reaction, injection site pain, injection site induration [169] ( <i>solution for injection only</i> ). Application site irritation [169] ( <i>suppositories only</i> ).
Rare:	

Edema [32,34], injection site necrosis [169] (*solution for injection only*).

\*The frequency reflects data from long-term treatment with a high dose (150 mg/day) [184].

**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) [184].

**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 [185].

## 8 Interactions

The following interactions include those observed with Cataflam solution for injection, sugarcoated tablets, suppositories, 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 [178,185].

***Lithium:*** If used concomitantly, diclofenac may raise plasma concentrations of lithium [27]. Monitoring of the serum lithium level is recommended [169].

***Digoxin:*** If used concomitantly, diclofenac may raise plasma concentrations of digoxin [28,29]. Monitoring of the serum digoxin level is recommended [174].

***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) [30,31,169].

***Ciclosporin and tacrolimus:*** Diclofenac, like other NSAIDs may increase the nephrotoxicity of ciclosporin and tacrolimus due to the effect on renal prostaglandins [55-58]. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin or tacrolimus [169,185].

***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) [169,179].

***Quinolone antibacterials:*** There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs [146].

## 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) [33,169].

***Anticoagulants and anti-platelet agents:*** Caution is recommended since concomitant administration could increase the risk of bleeding (see section 6 Warnings and precautions) [169]. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants [36-38], there are reports of an increased risk of hemorrhage in patients receiving diclofenac and anticoagulants concomitantly [59,185]. Close monitoring of such patients is therefore recommended [36-38,42].

**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) [169].

**Antidiabetics:** Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect [39-41]. 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.

There have also been isolated reports of metabolic acidosis when diclofenac was coadministered with metformin, especially in patients with pre-existing renal impairment [185].

**Phenytoin:** When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin [178].

**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 [17].

**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 [185].

## **9 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. 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 [186]. 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. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia, fetal renal impairment with subsequent oligohydramnios and/or premature closure of the ductus arteriosus (see sections 5 Contraindications and 13 Non-clinical safety data) [185].



## **Breast-feeding**

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 effects in the infant [16,26,61,169].

## **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 [169].

# **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 [169].

## **Therapeutic measures**

Management of acute poisoning with NSAIDs, including diclofenac essentially consists of supportive measures and symptomatic treatment [142-144]. 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 [143,169].

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 lifethreatening overdose [169] (*SCT only*).

# **11 Clinical pharmacology**

## **Pharmacotherapeutic group, ATC**

Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances (ATC code: M01A B05).

## **Mechanism of action (MOA)**

Cataflam contains potassium salt of diclofenac, a non-steroidal compound with pronounced antirheumatic, analgesic, anti-inflammatory, and antipyretic properties [1,3,43]. Inhibition of

prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action [21]. Prostaglandins play an important role in causing inflammation, pain, and fever.

Cataflam tablets and capsules have a rapid onset of action which makes them particularly suitable for the treatment of acute painful and inflammatory conditions [20] (*SCT and SC only*).

Diclofenac *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans [53,54].

### **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 edema [20,147-156].

#### **SCT and SC**

Clinical studies have also revealed that in primary dysmenorrhea the active substance is capable of relieving the pain and reducing the extent of bleeding [23,25,157,158].

In migraine attacks Cataflam has been shown to be effective in relieving the headache and in improving the accompanying symptoms nausea and vomiting [166,167].

#### **Suppositories**

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

### **Pharmacokinetics (PK)**

#### **Absorption**

##### **Solution for injection**

The absorption of diclofenac from the ampoules starts immediately after i.m. administration. On average, 80% of the mean maximum plasma concentration is attained within 10 minutes of administration.

The mean area under the plasma concentration/time curve (AUC) after parenteral administration is about twice as large as it is following oral or rectal administration of a dose of equal size while the mean maximum concentration is approximately 60% higher [52]. This difference in availability is attributable to the "first-pass" metabolism occurring when the drug is given orally or rectally.

##### **SCT**

Diclofenac is rapidly and completely absorbed from diclofenac potassium tablets [9,63]. The absorption sets in immediately after administration and the same amount is absorbed as from an equivalent dose of diclofenac sodium gastro-resistant tablets [11,63].

Mean peak plasma concentrations of 3.8 micro mol/L are attained after 20 to 60 minutes after ingestion of one tablet of 50 mg [11,63,64].

### **SC**

Diclofenac is rapidly and completely absorbed from diclofenac potassium soft capsules [183]. Mean peak plasma concentrations of 5.56 micromol/L are attained after 30 minutes following single oral administration of a 50 mg soft capsule [183].

### **SCT and SC**

Ingestion together with food has no influence on the amount of diclofenac absorbed although onset and rate of absorption may be slightly delayed [10,12,63].

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 [4,15,65].

### **Suppositories**

The administration of diclofenac potassium suppositories provides fast onset of absorption. After the administration of suppositories of 50 mg, peak plasma concentrations are attained on average within 1 hour, but maximal concentrations per dose unit are about 2/3 of those reached after administration of diclofenac potassium tablets [65,66,78,79].

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 [4,15,45].

The plasma concentrations attained in children given equivalent doses (mg/kg body weight) are similar to those obtained in adults [67].

### **For all formulations**

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed [16,63].

### **Distribution**

99.7% of diclofenac binds to serum proteins, mainly to albumin (99.4%) [8,68]. The apparent volume of distribution calculated is 0.12 to 0.17 L/kg [4,68,70].

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been reached [16]. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma levels, 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 [16,68,71,72].

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 [179].

## **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'-hydroxy4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates [6,7,68,73]

Two of these phenolic metabolites are biologically active, but to a much lesser extent than diclofenac [74].

## **Elimination**

Total systemic clearance of diclofenac from plasma is  $263 \pm 56$  mL/min (mean value  $\pm$  SD). The terminal half-life in plasma is 1 to 2 hours [4]. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours [75]. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a much longer plasma half-life. However, this metabolite is virtually inactive [73].

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 [7]. The rest of the dose is eliminated as metabolites through the bile in the faeces [18,68,76,77].

## **Linearity/non-linearity**

### **Solution for injection**

The plasma AUC values of diclofenac show a linear relationship to the size of the dose [15,16,63].

### **SCT**

The amount absorbed is in linear proportion to the size of the dose [11,15,63].

### **Suppositories**

The amount absorbed is in linear proportion to the size of the dose [66].

## **Special populations**

**Geriatric patients:** No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed [16,60,68,76,170].

**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 [5,13,68]. 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 [18].

**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 [19,68].

## 12 Clinical studies

Cataflam is a well established product.

## 13 Non-clinical safety data [182]

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 [171-173]. 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 [69,171].

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 5 Contraindications and 9 WOCBP, pregnancy, breastfeeding and fertility).

## 14 Pharmaceutical information

### Incompatibilities

#### Solution for injection

As a rule, Cataflam solution for intramuscular injection must not be mixed with other injection solutions.

#### SCT and SC

Not applicable.

#### Suppositories

Not applicable.

### Special precautions for storage

Do not store above 30°C.

Cataflam sugar-coated tablets must be protected from moisture.

Cataflam soft capsules must be protected from moisture and light. Store in the original package.

Cataflam solution for injection, sugar-coated tablets, soft capsules, and suppositories must be kept out of the reach and sight of children.

Information might differ in some countries.

## **Instructions for use and handling**

### **Solution for injection**

The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site.

To be injected by deep intragluteal injection into the upper outer quadrant using aseptic technique. Each ampoule is for single use only. The solution for injection should be used immediately after opening. Any unused contents should be discarded.

### **SCT and SC**

No special requirements.

### **Suppositories**

The suppositories should not be cut apart, as incorrect storage conditions may lead to uneven distribution of the active substance.

### **Special precautions for disposal** Country

specific.

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