NOVARTIS

Drug Regulatory Affairs

CATAFLAM®

(diclofenac potassium)

25 mg and 50 mg Sugar-coated tablets

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

Author(s): Jean-Michel Cahen, Sandra Jullian, Ariane Falconnier

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1 Name of the medicinal product

CATAFLAM® 25 mg sugar-coated tablets.

CATAFLAM® 50 mg sugar-coated tablets.

2 Qualitative and quantitative composition

The active substance is potassium-[o-[(2,6-dichlorophenyl)-amino]-phenyl]-acetate (= diclofenac potassium).

One sugar-coated 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 In Cataflam the sodium ion of diclofenac sodium (Voltaren®) has been replaced by a potassium ion.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Sugar-coated tablets.

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

Short-term treatment in the following acute conditions:

- Post-traumatic pain, inflammation and swelling, e.g. due to sprains [148].
- Post-operative pain, inflammation and swelling, e.g. following dental or orthopaedic surgery [20,149-156].
- Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea 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.

4.2 Posology and method of administration

As a general recommendation, the dose should be individually adjusted and the lowest effective dose given for the shortest possible duration [168].

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

Adults

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 in 2 to 3 doses.

In primary dysmenorrhoea, the daily dose should be individually adjusted and is generally 50 to 150 mg. A dose of 50 to 100 mg should be given initially and, if necessary, increased over the course of several menstrual cycles up to a maximum of 200 mg/day. 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.

Children and adolescents

Cataflam tablets are not recommended for use in children and adolescents below 14 years of age; other forms of diclofenac such as oral drops or suppositories could be used in these patients. For adolescents aged 14 years and over, a daily dose of 75 to 100 mg is usually sufficient. The total daily dose should generally be divided in 2 to 3 doses.

The maximum daily dose of 150 mg should not be exceeded [168].

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

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation [169].
- Last trimester of pregnancy (see section 4.6 Pregnancy and lactation) [169].
- Severe hepatic, renal and cardiac failure (see section 4.4 Special warnings and precautions for use) [169].
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Cataflam is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs [78,79].

4.4 Special warnings and precautions for use

Warnings

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 occur in patients receiving Cataflam, the medicinal product should be withdrawn [169].

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 4.8 Undesirable effects). 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.

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

Precautions

General

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 [169].

Caution is indicated in the elderly on basic medical grounds [81]. In particular it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

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.

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 oedema 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 [169].

Gastrointestinal effects

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 4.8 Undesirable effects). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage 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 haemorrhage 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 medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products 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 4.5 Interaction with other medicinal products and other forms of interaction) [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 4.8 Undesirable effects) [169].

Hepatic 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, 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].

Renal effects

As fluid retention and oedema 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 4.3 Contraindications) [44,169]. Monitoring of renal function is recommended as a precautionary measure when using Cataflam in such cases. Discontinuation of therapy is normally followed by recovery to the pre-treatment state.

Haematological 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, Cataflam may temporarily inhibit platelet aggregation [22,85]. Patients with defects of haemostasis should be carefully monitored [86,87].

4.5 Interaction with other medicinal products and other forms of interaction

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

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. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4 Special warnings and precautions for use) [30,31,169].

Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4 Special warnings and precautions for use) [33,169].

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4 Special warnings and precautions for use) [169]. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants [36-38], there are isolated reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly [59]. 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 4.4 Special warnings and precautions for use) [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 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.

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].

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin 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 [169].

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

Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism [178].

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

4.6 Pregnancy and lactation

Pregnancy

The use of diclofenac in pregnant women has not been studied. Therefore, Cataflam should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweights the risk to the foetus. 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 section 4.3 Contraindications). Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3 Preclinical safety data) [169].

Lactation

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].

4.7 Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking Cataflam should refrain from driving or using machines [169].

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

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

Table 1 [169]

Blood and lymphatic system disorders	
Very rare:	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis [24,125-130].
Immune system disorders	
Rare:	Hypersensitivity, anaphylactic and anaphylactoid reactions [131] (including hypotension and shock) [169].
Very rare:	Angioneurotic oedema (including face oedema) [169].
Psychiatric disorders	
Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common:	Headache, dizziness [24,32,34].
Rare:	Somnolence [34].
Very rare:	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis [32,34,101,102], taste disturbances [32,34,139,140], cerebrovascular accident [169].
Eye disorders	
Very rare:	Visual disturbance, vision blurred, diplopia [32,34,139,140].
Ear and labyrinth disorders	
Common:	Vertigo [24,32,34].
Very rare:	Tinnitus, hearing impaired [32,34,139,140].
Cardiac disorders	
Very rare:	Palpitations, chest pain, cardiac failure [81,136-138], myocardial infarction [169].
Vascular disorders	
Very rare:	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare:	Asthma (including dyspnoea).
Very rare:	Pneumonitis.
Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia [24,89].
Rare:	Gastritis [169], gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding

	or perforation) [24,32,34,89,90,93,96,97].
Very rare:	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis [89-96,98-100].
Hepatobiliary disorders	
Common:	Transaminases increased [24].
Rare:	Hepatitis, jaundice [120-123], liver disorder [169].
Very rare:	Fulminant hepatitis [124], hepatic necrosis, hepatic failure [176].
Skin and subcutaneous tissue disorders	
Common:	Rash [24,32,34].
Rare:	Urticaria [79,103].
Very rare:	Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura [104-110], pruritus [169].
Renal and urinary disorders	
Very rare:	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis [111-119].
General disorders and administration site conditions	
Rare:	Oedema [32,34].

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, 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 haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism [143].

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 [169].

5 Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of action

Cataflam contains the potassium salt of diclofenac, a non-steroidal compound with pronounced analgesic, anti-inflammatory and antipyretic properties [1,3,43]. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered to be fundamental to its mechanism of action [21]. 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 [20].

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

Pharmacodynamic effects

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 [20,147-156].

Clinical studies have also revealed that in primary dysmenorrhoea 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].

5.2 Pharmacokinetic properties

Absorption

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]. 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].

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

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].

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].

Biotransformation

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 [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 ± 56 mL/min (mean value ± 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].

Characteristics in patients

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

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].

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].

5.3 Preclinical 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 [171-173]. 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. The prenatal, perinatal and postnatal development of the offspring was not affected [69,171].

6 Pharmaceutical particulars

6.1 List of excipients

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.

Information might differ in some countries.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

Information might differ in some countries.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package.

Cataflam sugar-coated tablets must be kept out of the reach and sight of children.

Information might differ in some countries.

6.5 Nature and contents of container

Country specific.

6.6 Instructions for use/handling

No special requirements.

This is a non-referenced document.