# CATAFLAM®

## (diclofenac potassium)

## 25 mg and 50 mg Sugar-coated tablets

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

CATAFLAM 25 mg sugar-coated tablets.

CATAFLAM 50 mg sugar-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active substance**

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 In Cataflam the sodium ion of diclofenac sodium (Voltaren) has been replaced by a potassium ion.

Excipients with known effect: Sucrose

Each Cataflam 25mg tablet contain 45mg of Sucrose.

Each Cataflam 50mg tablet contain 67 mg of Sucrose.

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

## 3. PHARMACEUTICAL FORM

Sugar-coated tablets.

## 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.
- Post-operative pain, inflammation and swelling, e.g. following dental or orthopaedic surgery.
- Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis.
- Migraine attacks.
- 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. 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

Posology

As a general recommendation, the dose should be individually adjusted.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

### General target population: 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. An initial dose of 50 mg is usually sufficient. If necessary, and initial dose of 100mg can be prescribed with a maximum of 200mg/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.

**Special populations**

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

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 12.5mg and 25mg 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. The total daily dose should generally be divided in 2 to 3 doses.

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

**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 4.4 Special warnings and precautions for use).

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

Patients with congestive heart failure (NYHA-I) or significant risk factors for cardiovascular disease should be treated with Cataflam only after careful consideration and only at doses ≤100mg daily if treated for more than 4 weeks (see section 4.4 Special warnings and precautions for use).

**Renal impairment**

Cataflam is contraindicated in patients with renal failure (GFR<15mL/min./1.73m$^2$) (see section 4.3 Contraindications).No specific studies have been carried out in patients with renal impairment, therefore, no specific dose recommendations can be made. Caution is advised when administering Cataflam to patients with renal impairment (see section 4.4 Special warnings and precautions for use).

**Hepatic impairment**

Cataflam is contraindicated in patients with hepatic failure see section 4.3 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 4.4 Special warnings and precautions for use).

Method of administration

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

## 4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Last trimester of pregnancy (see section 4.6 Fertility, pregnancy and lactation).
- Hepatic failure
- Renal failure (GFR<15mL/min./1.73m$^2$)
- 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 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).
- Established congestive heart failure (NYHA II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

## 4.4 Special warnings and precautions for use

**General**

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 Dosage and administration, and GI and cardiovascular risks below).

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.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

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

Cataflam tablets contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

**Gastrointestinal effects**

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

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

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. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

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)/aspirin 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 4.5 Interaction with other medicinal products and other forms of interaction).

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).

**Masking signs of infections**

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

**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, 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.

**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, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3 Contraindications). 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.

**Skin effects**

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 NSAIDSs (see 4.8 Undesirable effects). Patients appear to be at highest risk for 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.

**Cardiovascular and cerebrovascular effects**

Appropriate monitoring and advice are required for patients with a history of hypertension and/or congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy.

Patients with congestive heart failure (NYHA-I) and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration and only at doses ≤100mg daily when treatment continues for more than 4 weeks.
As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically especially when treatment continues for more than 4 weeks.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur

without warnings. Patients should be instructed to see a physician immediately in case of such an event.

**Hematologic effects**
Use of Cataflam sugar coated tablets is recommended only for short term treatment. During prolonged treatment with Diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

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

**Geriatric patients**

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

**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.

**Interactions with NSAIDs**

The concomitant use of Cataflam with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to undesirable effects (see section 4.5 Interactions with other medicinal products and other forms of interactions).

## 4.5 Interactions with other medicinal products and other forms of interactions

The following interactions include those observed with Cataflam sugar-coated tablets 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. 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. 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 4.4 Special warnings and precautions for use).

***Ciclosporin and tacrolimus:*** Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin 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 should be avoided since they may increase the frequency of gastrointestinal undesirable effects (see section 4.4 Special warnings and precautions for use).

***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). 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 4.4 Special warnings and precautions for use).

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

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

***Methotrexate:*** Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. 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.

***Phenytoin:*** When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.
***Colestipol and cholestyramine***: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.
***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).

## 4.6 Fertility, pregnancy and lactation

**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.

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 4.3 Contraindications and 5.3 Non-clinical safety data).
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %.
The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.
In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. During the first and second trimester of pregnancy, Cataflam should not be given unless clearly necessary. If Cataflam is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios is found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose

the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; (see above)

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Cataflam is contraindicated during the third trimester of pregnancy.

**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 .

**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.

## 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.

## 4.8 Undesirable effects

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 (Table 1) 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, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000),not known: cannot be estimated from the available data..

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**

| | |
|---|---|
| **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. |
| 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 and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, esophageal disorder, intestinal diaphragm disease, pancreatitis. |
| Not known | Ischaemic colitis |
| **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 (150mg/day).

**Description of selected adverse drug reactions**

**Arteriothrombotic events**

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment (see sections 4.3 and 4.4 for Contraindications and Special Warnings and precautions for use).

**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 vison. If such symptoms occur during diclofenac treatment an ophthalmological examination may be considered to exclude other causes.

**Reporting of suspected adverse reactions**

**g of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

## 4.9 Overdose

**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.

## 5 CLINICAL PHARMACOLOGY

### 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 (MOA)**

Cataflam contains the potassium salt of diclofenac, a non-steroidal compound with pronounced antirheumatic analgesic, anti-inflammatory and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered to be 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 the concentrations reached in humans.

**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.

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.

### 5.2 Pharmacokinetic properties

**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 gastro-resistant tablets.

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

**Distribution**

99.7% of diclofenac binds 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 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.

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

**Biotransformation/metabolism**

Biotransformation of diclofenac 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 faeces.

**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.

**Clinical studies**

Cataflam is a well-established product.

### 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. In standard preclinical animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

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

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors (see sections 5 Contraindications and 9 WOCBP, pregnancy, breast-feeding and fertility).

## 6 PHARMACEUTICAL INFORMATION

### 6.1 List of excipients

**Core:** Silica aerogel; calcium phosphate; magnesium stearate; pregelatinized maize starch; polyvidone; sodium carboxymethyl starch.

**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.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store below 30°C.

Cataflam sugar-coated tablets must be protected from moisture. Store in the original package.

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

### 6.5 Nature and contents of container

Aluminium blisters PVC/PE/PVDC.

Pack size/s: 20, 28, 30 tablets

Not all pack sizes may be marketed.

### 6.6 Instructions for use and handling

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Novartis Ireland Limited
Vista Building,
Elm Park, Merrion Road,
Ballsbridge, Dublin 4,
Ireland.

## 8. MARKETING AUTHORISATION NUMBER

Cataflam 25mg coated tablets: MA1249/00201
Cataflam 50mg coated tablets: MA1249/00202

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th July 2005
Date of latest renewal: 29th April 2013

## 10. DATE OF REVISION OF THE TEXT

17/09/2024