Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cataflam Sachets 50 mg Powder for Oral Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One sachet contains 50mg diclofenac potassium

The sachet also contains 50 mg aspartame (E951)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for oral solution.
White to light yellow powder for oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short-term treatment of all grades of pain and inflammation in the following acute conditions:

- Post-traumatic pain, inflammation and swelling, e.g. due to sprains.
- Acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder).
- 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 and associated menorrhagia.
- 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

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

The contents of the sachet should be dissolved with stirring in a glass of natural (non-carbonated) water. The solution may remain slightly opalescent, but this should not influence the efficacy of the preparation. The solution should be swallowed preferably before meals.

Adults
The recommended initial dosage is 100 to 150mg. In milder cases 50 to 100mg daily are usually sufficient.

The daily dosage should generally be divided in 2 to 3 doses.

In primary dysmenorrhoea, the daily dosage should be individually adjusted and is generally 50 to 150mg. Initially a dose of 50 to 100mg should be given 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 50mg 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 50mg may be taken. If needed, further doses of 50mg may be taken at intervals of 4 to 6 hours, not exceeding a total dose of 200mg per day.

Children and adolescents

Cataflam 50mg powder for oral solution is 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 12.5mg are available.

For adolescents aged 14 years and over, 50 to 100mg daily are usually sufficient, given as 1 to 2 divided doses.

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

The use of Cataflam 50mg powder for oral solution in migraine attacks has not been established in children and adolescents.

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- 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 Pregnancy and lactation).*
- Severe hepatic, renal or heart failure *(see section 4.4 Special warnings and precautions for use).*
- 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.

4.4 Special warnings and precautions for use

Warnings

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal *(see section 4.2 Posology and method of administration).* When gastrointestinal bleeding or ulceration occurs in patients receiving Cataflam, the medicinal product should be withdrawn.

Serious skin reaction, 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 a highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment.

Cataflam should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

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

Like other NSAIDs, Cataflam may mask the signs and symptoms of infection due to its pharmacodynamic properties. The use of diclofenac sodium 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, withdrawl of diclofenac sodium should be considered.

Precautions

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest possible duration necessary to control symptoms *(see section 4.2 Posology & method of administration)* and gastrointestinal and cardiovascular risks below.

The use of Cataflam with concomitant 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.

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

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.

Gastrointestinal effects

As with all NSAIDs, 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, ulceration or perforation is higher with increasing NSAID doses in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation *(see section 4.3 Contra-indications)* and in the elderly. These patients should commence treatment on the lowest dose available.

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 *(see below and section 4.5 Interactions with other medicinal products and other forms of interactions).*

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, anti-platelet agents such as aspirin or selective serotonin-reuptake inhibitors *(see section 4.5 Interaction with other medicinal products and other forms of interaction).*

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis or Crohn's disease), as their condition may be exacerbated *(See section 4.8 Undesirable effects).*

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that the use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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, values of one or more liver enzymes may increase. During prolonged treatments 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, etc.), Cataflam should be discontinued. Hepatitis may occur without prodromal symptoms.

Caution is called for when using Cataflam on 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, history of hypertension, the elderly, patients receiving concomitant treatment being treated 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 usually 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, as with other NSAIDs, monitoring of the blood count is recommended.

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

Cataflam 50mg powder for oral solution contains aspartame, a source of phenylalanine which may be harmful for patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

(Including interactions observed with other dosage forms of diclofenac potassium and diclofenac sodium).

Lithium: If used concomitantly, diclofenac may increase 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 drugs (e.g. beta- blockers, angiotensin converting enzyme (ACE) inhibitor) 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 diuretics may be associated with increased serum potassium levels, which should therefore be monitored frequently *(see section 4.4 Special warnings and precautions for use).*

Anticoagulants: Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, NSAIDs may enhance the effects of anti-coagulants, such as warfarin *(see section 4.4.).* There are also isolated reports of an increased risk of haemorrhage 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 and SSRIs may increase the risk of gastrointestinal bleeding *(see section 4.4 Special warning 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, isolated 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 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.

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

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

Other NSAIDs and Corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or oral corticosteroids may increase the risk of gastrointestinal ulceration or bleeding (*see section 4.4 Special warnings and precautions for use).*

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 outweighs the risk to the foetus. As with other NSAIDs, use 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/fetal development, parturition or postnatal development *(see section 5.3 Preclinical safety data).*

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 dizziness, vertigo, somnolence or other central nervous system disturbances while taking Cataflam including visual disturbances, should not drive or operate machines.

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).

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur *(see section 4.4 Special warnings and precautions for use).* Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease *(see section 4.4 Special warnings and precautions for use)* have been reported following administration. Less frequently, gastritis has been observed.

The following table of 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 leucopenia, anaemia (including haemolytic anaemia and aplastic anaemia), agranulocytosis.
Immune system disorder	
Rare:	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock)
Very rare:	Angioneurotic oedema (including face oedema).
Psychiatric disorders:	
Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common:	Headache, dizziness,
Rare:	Somnolence,
Very rare:	Paraesthesias, memory impairment, convulsion, anxiety, Tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Eye disorders	
Very rare:	Visual disturbance, vision blurred, diplopia.
Ear and labyrinth disorders	
Common:	Vertigo.
Very rare:	Tinnitus, hearing impaired.

Cardiac disorders:	
Very rare:	Palpitations, chest pain, cardiac failure, myocardial infarction
Vascular disorders	
Very rare:	hypertension, vasculitis.
Respiratory, thoracic and mediastinal disoders:	
Rare:	Asthma (including dyspnoea).
Very rare:	Pneumonitis.
Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain,flatulence, anorexia.
Rare:	Gastritis, gastrointestinal haemorrhage, haematemesis,diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation).
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.
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 eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necroylsis (Lyell's syndrome), dermatitis exfoliative loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders	
Very rare:	Acute renal failure haematuria, proteinuria, nephritic syndrome, interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare:	Oedema.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that the use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) *(see section 4.4 Special warnings and precautions for use).*

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.

Therapeutic measures

Management of acute poisoning with NSAIDS consists essentially 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 haemoperfusion are probably unlikely to be helpful in accelerating the elimination of NSAIDs because of their high protein binding rate 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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Cataflam sachets contain the potassium salt of diclofenac, a non-steroidal compound with pronounced analgesic, anti-inflammatory, and antipyretic properties.

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

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

Pharmacodynamic effects

Cataflam sachets have 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 sachets have 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. Mean peak plasma concentrations of 5.5 micromol/L are attained after 5 - 20 minutes after ingestion of one sachet of 50 mg.

Ingestion together with food is expected to have no influence on the amount of diclofenac absorbed although onset and rate of absorption may be slightly delayed.

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

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 0.12-0.17 L/kg.

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

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. 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 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 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.

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

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.

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

5.3 Preclinical safety data

Preclinical data form 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. There was no evidence the diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac had no influence on the fertility of the parent animals in rats. The prenatal, perinatal, and postnatal development of the offspring was not affected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium hydrogen carbonate
Mannitol
Aspartame
Saccharin sodium

Glyceryl dibehenate
Mint flavour
Anise flavour

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with anything other than water.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Sachet consisting of coupled paper/aluminium/polyethylene, hermetically sealed in four directions Three sachets are packaged in one carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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