Abbreviated Prescribing Information based on NCDS 08:

Rapiflam Tablets

Composition: Each film-coated tablet contains: 25 or 50 mg of Diclofenac Potassium. Excipients: lactose monohydrate, maize starch, cellulose microcrystalline,povidone, crospovidone, magnesium stearate,colloidal silica , purified talc, opadry white, red iron oxide. **Indication**: For treatment of : Rheumatoid arthritis, Osteoarthrosis, Low back pain, Migraine attacks, Acute musculo-skeletal disorders and trauma such as periarthritis (especially frozen shoulder), tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations; relief of pain in fractures, Ankylosing spondylitis, Acute gout, Control of pain and inflammation in orthopaedic, dental and other minor surgery, Pyrophosphate arthropathy and associated disorders. **Dosage and administration**: Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. For oral administration **Adults:** The minimal effective dose should be administered. The recommended daily dose is 100-150 mg in two or three divided doses. For milder cases, 75-100 mg daily in two or three divided doses is usually sufficient. In migraine an initial dose of 50 mg should be taken at the first signs of an impending attack. In cases where relief 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 4-6 hours, not exceeding a total dose of 200 mg per day. **Children:** For children over 14 years of age, the recommended daily dose is 75-100 mg in two or three divided doses. Diclofenac potassium 25 mg film-coated tablet and 50 mg film-coated tablet are not recommended for children under 14 years of age. The use of diclofenac potassium tablets in migraine attacks has not been stablished in children. **Elderly:** Dosage adjustment is not necessary in the elderly. Although the pharmacokinetics of diclofenac are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight and the patient should be monitored for gastrointestinal bleeding for 4 weeks following initiation of NSAID therapy. **Cardiovascular and significant cardiovascular risk factors:** Diclofenac is contraindicated in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. Patients with congestive heart failure (NYHA-I) or significant risk factors for cardiovascular disease should be treated with diclofenac only after careful consideration. Since cardiovascular risks with diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used and for the shortest duration possible. **Renal impairment:** Diclofenac is contraindicated in patients with renal failure. No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with renal impairment. **Hepatic impairment:** Diclofenac is contraindicated in patients with hepatic failure. 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 diclofenac to patients with mild to moderate hepatic impairment**. Contraindications :** Diclofenac, administered systemically, is contraindicated in: 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 NSAID therapy, active, or

history of recurrent peptic ulcer/ haemorrhage (two or more distinct episodes of proven ulceration or bleeding), last trimester of pregnancy, hepatic failure, renal failure, established congestive heart failure (NYHA II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease. Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is contraindicated in patients in whom attacks of asthma, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs (e.g. ibuprofen). **Special warnings & precautions for use:** *Undesirable effects:* Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. *Use of diclofenac with systemic nonsteroidal anti-inflammatory drugs (NSAIDs):* The concomitant use of diclofenac 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. *Elderly:* 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. *Allergic reactions:* As with other NSAIDs, allergic reactions, including anaphylactic/ anaphylactoid reactions, can also occur 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. *Infection:* Like other NSAIDs, diclofenac may mask the signs and symptoms of the infection due to its pharmacodynamic properties. *Gastrointestinal effects:* Gastrointestinal bleeding (haematemesis, melaena), 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 medicinal product should be withdrawn. As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation. The elderly has an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. To reduce the risk of gastrointestinal 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. 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. Patients with a history of gastrointestinal toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, such as warfarin, anti-platelet agents, such as acetylsalicylic acid or selective serotonin-reuptake inhibitors. Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as these conditions may be exacerbated. 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. *Hepatic effects:* Close medical surveillance is required when prescribing diclofenac 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 diclofenac, 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), diclofenac should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms. Caution is called for when using diclofenac 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. Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation of therapy is usually 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 NSAIDs including diclofenac. Patients appear to be at the 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. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. *Cardiovascular risk:* Patients with congestive heart failure (NYHA-I) or patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. 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. Appropriate monitoring and advice are required for patients with a history of hypertension and congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy including diclofenac. 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. 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. *Haematological effects:* During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended. Diclofenac may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored. *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. Like other drugs that inhibit prostaglandin synthetase activity, diclofenac and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma. *Systemic lupus erythematosus (SLE) and mixed connective*

tissue disease : In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis*. Lactose:* Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose and galactose malabsorption should not take this medicine. **Interactions:** ***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 agents (e.g., beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis. 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. ***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. ***Other NSAID including cyclooxygenase-2 selective inhibitors and corticosteroids:*** Concomitant administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs. ***Anticoagulants and anti-platelet agents:*** Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. -Close monitoring of such patients is therefore recommended. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation. ***Selective serotonin reuptake inhibitors (SSRIs):*** Concomitant administration of SSRIs may increase the risk of gastrointestinal. ***Antidiabetics:*** Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy. ***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 treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID. ***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. ***Tacrolimus:*** Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor. ***Quinolone antibacterials:*** Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an

NSAID. ***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. ***Cardiac glycosides:*** Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and increase plasma glycoside levels. ***Mifepristone:*** NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone. ***Potent CYP2C9 inhibitors:*** Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac metabolism. **Pregnancy & lactation:** ***Fertility:*** As with other NSAIDs, the use of diclofenac 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 diclofenac should be considered. ***Pregnancy:*** If diclofenac is used by a woman attempting to conceive, or during the first trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Diclofenac is contraindicated during the third trimester of pregnancy. 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 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. 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. At the end of the pregnancy all prostaglandin synthesis inhibitors may expose the mother and the neonate 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. ***Lactation:*** Diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant. Like other NSAIDs, diclofenac passes into the breast milk in small amounts. **Ability to perform tasks that require judgement, motor or cognitive skills:** Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness or fatigue while taking NSAIDs should refrain from driving or operating machinery. **Adverse Reactions:** ***Infections and infestations****: Not known:* injection site necrosis (for intramuscular injection formulation only). ***Blood and lymphatic system disorders****: Very rare:* thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis. ***Immune system disorders****: Rare:* hypersensitivity, anaphylactic reaction, anaphylactoid reaction (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, tiredness. *Very rare*: paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident. *Not Known*: confusion, hallucinations, disturbances of

sensation, malaise. ***Eye disorders****: Very rare:* visual disturbance, vision blurred, diplopia. *Unknown:* optic neuritis. ***Ear and labyrinth disorders****: Common:* vertigo. *Very rare:* tinnitus, hearing impaired. ***Cardiac disorders****:* Uncommon (The frequency reflects data from long-term treatment with a high dose (150 mg/day) palpitations, chest pain, cardiac failure, myocardial infarction. *Not known:* Kounis syndrome. ***Vascular disorders****: Very rare*: hypertension, hypotension, vasculitis. ***Respiratory, thoracic and mediastinal disorders:*** *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 (sometimes fatal particularly in the elderly). *Very rare:* colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, 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 eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (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, nephrotic syndrome, interstitial nephritis, renal papillary necrosis. ***Reproductive system and breast disorders****: Very rare:* impotence. **Overdose:** ***Symptoms and signs:*** There is no typical clinical picture resulting from diclofenac overdosage. It can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible. ***Treatment:*** 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 haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to high protein binding and extensive metabolism. Activated charcoal may be considered after ingestion of a potentially toxic overdose. Further management should be as clinically indicated or as recommended by the national poisons centre, where available. **Storage**: Store at temperature not exceeding 30^0C, in a dry place. **Full Prescribing Information is available on request. Please read t he full prescribing information prior to administration.**