1. Name of Medicinal Product

MYSROTEC (DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS)

2. Qualitative & Quantitative Composition

Each film-coated tablets contains:
Misoprostol USP 200 mcg
(As 1% HPMC Dispersion)
Diclofenac sodium BP 75 mg
Colour……..Titanium dioxide BP
Excipients……QS

3 Pharmaceutical form

Film-coated tablets

White colour, round shape biconvex, film coated tablet.

4.1 Therapeutic Indications

DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS is indicated for adult patients who require the non-steroidal anti-inflammatory drug diclofenac together with misoprostol.

The diclofenac component of DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS is indicated for the symptomatic treatment of osteoarthritis and rheumatoid arthritis. The misoprostol component of DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS is indicated for patients with a special need for the prophylaxis of NSAID-induced gastric and duodenal ulceration.

4.2 Posology and method of administration
Posology

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

Adults

One tablet to be taken with food, two times daily.

Elderly/renal, cardiac and hepatic impairment

No adjustment of dosage is necessary in the elderly or in patients with hepatic impairment or mild to moderate renal impairment as pharmacokinetics are not altered to any clinically relevant extent. Nevertheless, elderly patients and patients with renal, cardiac or hepatic impairment should be closely monitored (see sections 4.4 and 4.8).

Paediatric population

The safety and efficacy of DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS in children under 18 years has not been established.

Method of administration

Tablets should be taken with food and swallowed whole without chewing.

4.3 Contraindications

DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS is contraindicated in:

- Patients with active peptic ulcer/haemorrhage or perforation or who have active GI bleeding or other active bleedings e.g. cerebrovascular bleedings.

- Pregnant women and in women planning a pregnancy (see section 4.6)

- Women of childbearing potential who are not using effective contraception (see sections 4.4, 4.6 and 4.8).

- Patients with a known hypersensitivity to diclofenac, acetylsalicylic acid, other NSAIDs, misoprostol, other prostaglandins, or any other ingredient of the product.

- Patients in whom, attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory agents.

- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

- Patients with severe renal and hepatic failure.

- 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

Warnings

The use of diclofenac/misoprostol with concomitant systemic NSAIDs including COX-2 inhibitors should be avoided, except for patients requiring low dose acetylsalicylic acid – caution is advised in such patients with close monitoring. Concomitant use of a systemic NSAID and another systemic NSAID may increase frequency of gastrointestinal ulcers and bleeding.

In women of childbearing potential (see also section 4.3)

DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS must not be used unless they use effective contraception and have been advised of the risks of taking the product if pregnant (see section 4.6).

The label will state: 'Not for use in women of childbearing potential unless using effective contraception'.

Precautions

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

Renal/cardiac/hepatic impairment

In patients with renal, cardiac or hepatic impairment and in the elderly, caution is required since the use of NSAIDs may result in deterioration of renal function. In the following conditions DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS should be used only in exceptional circumstances and with close clinical monitoring: advanced liver disease, severe dehydration.

In a large trial where patients received diclofenac for a mean of 18 months, ALT/AST elevations were observed in 3.1% of patients. ALT/AST elevations usually occur within 1-6 months. In clinical trials, hepatitis has been observed in patients who received diclofenac, and in post-marketing experience, other hepatic reactions have been reported, including jaundice and hepatic failure. During diclofenac/misoprostol therapy, liver function should be monitored periodically. If diclofenac/misoprostol is used in the presence of impaired liver function, close monitoring is necessary. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, treatment with diclofenac should be discontinued.

Diclofenac metabolites are eliminated primarily by the kidneys (see section 5.2). The extent to which the metabolites may accumulate in patients with renal failure has not been studied. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

In rare cases, NSAIDs, including diclofenac/misoprostol, may cause interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. NSAIDs inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of an NSAID may precipitate overt renal decompensation, which is typically followed by recovery to pretreatment state upon discontinuation of NSAID therapy. Patients at greatest risk of such a reaction are those with congestive heart failure, liver cirrhosis, nephrotic syndrome overt renal disease and the elderly. Such patients should be carefully monitored while receiving NSAID therapy.

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.

As with all NSAIDS, diclofenac/misoprostol can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. NSAIDs, including diclofenac/misoprostol, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with diclofenac/misoprostol and throughout the course of therapy.

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.

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

Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur (see section 4.3).

Blood system/gastrointestinal

NSAIDs, including diclofenac/misoprostol, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. When GI bleeding or ulceration occurs in patients receiving diclofenac/misoprostol, the treatment should be withdrawn. These events can occur at any time during treatment, with or without warning symptoms or in patients with a previous history of serious GI events.

Patients most at risk of developing these types of GI complications with NSAIDs are those treated at higher doses, the elderly, patients with cardiovascular disease, patients using concomitant acetylsalicylic acid, corticosteroids, selective serotonin reuptake inhibitors, patients who consume alcohol or patients with a prior history of, or active, gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions.

Therefore, diclofenac/misoprostol should be used with caution in these patients and commence on treatment at the lowest dose available (see section 4.3).

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.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, , selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5). The concomitant use of NSAIDs, including DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS, with oral anticoagulants increases the risk of GI and non-GI bleeding and should be given with caution. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban). Anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant (see section 4.5).

DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS in common with other NSAIDs, may decrease platelet aggregation and prolong bleeding time. Extra supervision is recommended in haematopoietic disorders or in conditions with defective coagulation or in patients with a history of cerebrovascular bleeding.

Caution is required in patients suffering from ulcerative colitis or Crohn's Disease as these conditions may be exacerbated (see section 4.8).

Care should be taken in elderly patients and in patients treated with corticosteroids, other NSAIDs, or anti-coagulants (see section 4.5).

Skin reactions

Serious skin reactions, some of them fatal, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including diclofenac/misoprostol (see section 4.8). Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Diclofenac/misoprostol should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Hypersensitivity

NSAIDs may precipitate bronchospasm in patients suffering from, or with a history of bronchial asthma or allergic disease.

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.

Long-term treatment

All patients who are receiving long-term treatment with NSAIDs should be monitored as a precautionary measure (e.g. renal, hepatic function and blood counts). During long-term, high dose treatment with analgesic/anti-inflammatory drugs, headaches can occur which must not be treated with higher doses of the medicinal product.

• This tablets may mask fever and thus an underlying infection.

• Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium content

This tablet contains less than 1 mmol sodium (23 mg) per tablet. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

Hydrogenated castor oil

This tablet also contains hydrogenated castor oil, which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

NSAIDs may attenuate the natriuretic efficacy of diuretics due to inhibition of intrarenal synthesis of prostaglandins. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels; hence serum potassium should be monitored.

Because of their effect on renal prostaglandins, NSAIDs such as diclofenac may increase the nephrotoxicity of ciclosporin. When co-administered with ciclosporin, there is a two-fold increase in diclofenac systemic exposure. It is prudent to start with the lowest dose of DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS and to monitor closely for signs of toxicity.

There is a possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Steady state plasma lithium and digoxin levels may be increased and ketoconazole levels may be decreased.

Pharmacodynamic studies with diclofenac have shown no potentiation of oral hypoglycaemic and anticoagulant drugs. However as interactions have been reported with other NSAIDs, caution and adequate monitoring are, nevertheless advised (see statement on platelet aggregation in Precautions).

Because of decreased platelet aggregation caution is advised when using DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS with anti-coagulants. NSAIDs may enhance the effects of anti-coagulants, such as warfarin, aniplatelet agents, such as acetylsalicylic acid, and serotonin re-uptake inhibitors (SSRIs) thereby increasing the risk of gastrointestinal bleeding (see section 4.4).

When diclofenac was administered with acetylsalicylic acid, the protein binding of diclofenac was reduced, although the clearance of the free diclofenac was not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac/misoprostol and acetylsalicylic acid is not generally recommended because of the potential risk of increased gastrointestinal adverse effects.

Cases of hypo and hyperglycaemia have been reported when diclofenac was associated with antidiabetic agents.

Caution is advised when methotrexate is administered concurrently with NSAIDs because of possible enhancement of its toxicity by the NSAID as a result of increase in methotrexate plasma levels especially in patients receiving high doses of methotrexate.

Concomitant use with other NSAIDs or with corticosteroids may increase the frequency of gastrointestinal ulceration or bleeding and of side effects generally.

Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists (AIIA) and beta-blockers: NSAIDs can reduce the efficacy of diuretics and other antihypertensive drugs, including ACE inhibitors, AIIA and beta-blockers.

In patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or an AIIA and/or diuretics with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible. The occurrence of these interactions should be considered in patients taking diclofenac/misoprostol with an ACE inhibitor or an AIIA and/or diuretics.

Antacids may delay the absorption of diclofenac. Magnesium-containing antacids have been shown to exacerbate misoprostol-associated diarrhoea.

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Caution is recommended when co-prescribing diclofenac with mild 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. Caution is also recommended when co-prescribing diclofenac with moderate CYP2C9 inhibitors (such as fluconazole, miconazole and amiodarone). Concomitant administration of diclofenac with these moderate CYP2C9 inhibitors has not been studied, but is expected to lead to a larger magnitude of interaction.

Voriconazole increased C_{max} and AUC of diclofenac (50 mg single-dose) by 114% and 78%, respectively.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must be informed about the risk of teratogenicity prior to treatment with diclofenac-misoprostol. Treatment must not be initiated until pregnancy is excluded, and women should be fully counselled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, treatment must be immediately discontinued (see sections 4.3, 4.4 and 4.8).

Pregnancy

DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS is contraindicated in pregnant women and in women planning a pregnancy.

Misoprostol:

Misoprostol induces uterine contractions and is associated with abortion, premature birth, foetal death and foetal malformations. Approximately a 3-fold increased risk of malformations was reported in pregnancies exposed to misoprostol during the first trimester, compared to a control group incidence of 2%. In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of suckling and deglutition and eye movements, with or without limb defects); amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, olygodactyly, cleft palate inter alia) and central nervous system anomalies (cerebral and cranial anomalies as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects). Other defects including arthrogryposis have been observed.

Consequently:

- Women should be informed of the risk of teratogenicity.

- Should the patient wish to continue with her pregnancy after exposure of misoprostol *in utero*, a careful ultrasound scan monitoring of the pregnancy, with special attention to the limbs and head must be carried out.

Diclofenac:

Inhibition of prostaglandin synthesis might adversely affect 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 prostaglandin synthesis inhibitors 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 prostaglandin synthesis inhibitors 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.

During the second or third trimester of pregnancy, NSAIDs may expose the foetus to:

- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis. Such effects may occur shortly after treatment initiation and are usually reversible upon discontinuation.

- In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

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

- Cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);

- Renal dysfunction (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;

Breast-feeding

Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. Diclofenac is excreted in breast milk in very small quantities. In general, the potential effects on the infant from any exposure to misoprostol and its metabolites via breast feeding are unknown. However, diarrhoea is a recognised side effect of misoprostol and could occur in infants of nursing mothers. DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS should therefore not be administered to nursing mothers.

Fertility

Based on the mechanism of action, the use of NSAIDs, including diclofenac/misoprostol, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including diclofenac/misoprostol, should be considered.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness or other central nervous system disturbances while taking NSAIDs should refrain from driving or operating machinery. This tablet has minor influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In the table below the incidence of adverse drug reactions reported in controlled clinical studies where this tablet was administered to more than 2,000 patients are listed. Additionally, adverse drug reactions have been identified during post-marketing surviellance and the frequency of some ADRs cannot be estimated from the available data. The most commonly observed adverse events are gastrointestinal in nature. In general, the adverse event profile of diclofenac/misoprostol in patients 65 years of age and older (556 subjects) was similar to that of younger patients (1,564 subjects). The only clinically relevant differences were that patients 65 years of age and older appeared to be less tolerant to the gastrointestinal effects of diclofenac/misoprostol given three times a day.

Tabulated list of adverse reactions

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 and < 1/10)**	**Uncommon (≥ 1/1,000 and < 1/100)**	**Rare (≥ 1/10,000 and < 1/1,000)**	**Very rare (< 1/10,000)**	**Not known**
Infections and infestations			Vaginal infection			
Blood and lymphatic system disorders			Thrombo-cytopenia, leucopenia			Aplastic anaemia, agranulocytosis, haemolytic anaemia, platelet aggregation inhibition
Immune system disorders			Hypersensiti-vity	Anaphylactic reaction		
Metabolism and nutrition disorders			Decreased appetite			Fluid retention
Psychiatric disorders		Insomnia	Depression, anxiety	Nightmares		Psychotic disorder, disorientation, mood altered, irritability
Nervous system disorders		Headache, dizziness	Cerebrovascular accident, somnolence, tremor, paraesthesia			Meningitis aseptic[1], convulsion, memory impairment, dysgeusia
Eyes disorders			Vision blurred			Visual impairment
Ear and labyrinth			Tinnitus			

disorders						
Cardiac disorders			Cardiac failure, myocardial infarction, palpitations			Kounis syndrome
Vascular disorders			Hypertension	Hypotension		Shock, vasculitis
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Pneumonitis		Asthma
Gastrointestinal disorders	Abdominal pain, diarrhoea[2], nausea, dyspepsia	Gastritis, vomiting, flatulence, eructation, constipation, peptic ulcer, gastrointestinal inflammation, gastrointestinal ulcer, duodenitis, oesophagitis	Stomatitis, melaena, mouth ulceration, dry mouth, gastrointestinal bleeding[3]	Pancreatitis, haematemesis, colitis, oesophageal disorder, glossitis		Gastrointestinal perforation[3], Crohn's disease, tongue oedema
Hepatobiliary disorders				Hepatitis, jaundice	Hepatic failure	Hepatitis fulminant
Skin and subcutaneous tissue disorders		Rash, pruritus	Purpura, urticaria	Angioedema, dermatitis bullous, photosensitivity reaction, alopecia		Erythema multiforme, toxic epidermal necrolysis[4], Stevens-Johnson syndrome[4], dermatitis exfoliative[4], Henoch Schonlein purpura, mucocutaneous rash, rash vesicular, DRESS Syndrome
Renal and urinary disorders						Renal failure, renal failure acute, renal papillary necrosis,

						tubulointerstitial nephritis, nephrotic syndrome, proteinuria, haematuria, glomerulonephritis, glomerulonephritis minimal lesion, glomerulonephritis membranous, renal impairment
Pregnancy, puerperium and perinatal conditions						Foetal death, abortion incomplete, premature baby, anaphylactoid syndrome of pregnancy, retained placenta or membranes, uterine contractions abnormal
Reproductive system and breast disorders			Menorrhagia, metrorrhagia, vaginal haemorrhage, postmenopausal haemorrhage, menstrual disorder	Breast pain, dysmenorr-hoea		Uterine haemorrhage, uterine spasm, infertility (female fertility decreased)
Congenital, familial and genetic disorders		Foetal malformati-ons				
General disorders and administration site conditions			Chest pain, face oedema, oedema[5], pyrexia, chills, fatigue			Inflammation
Investigations		Alanine amino-	Blood bilirubim increased,			

		transferase increased, blood alkaline phosphatase increased, haematocrit decreased	aspartate aminotransferase increased			
Injury, poisoning and procedural complications						Uterine rupture, uterine perforation

[1] Symptoms of aseptic meningitis (stiff neck, headache, nausea, vomiting, fever or impaired consciousness) have been reported during treatment with NSAIDs. Patients suffering from autoimmune disease (e.g. lupus erythematosus, mixed connective tissue disorders) seem to be more susceptible.

[2] Diarrhoea is usually mild to moderate and transient and can be minimised by taking DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS with food and by avoiding the use of predominantly magnesium-containing antacids.

[3] GI perforation or bleeding can sometimes be fatal, particularly in the elderly (see section 4.4).

[4] Serious skin reactions, some of them fatal, have been reported very rarely (see section 4.4).

[5] Especially in patients with hypertension or impaired renal function (see section 4.4).

Given the lack of precise and/or reliable denominator and numerator figures, the spontaneous adverse event reporting system through which post marketing safety data are collected does not allow for a medically meaningful *frequency of occurrence* of any undesirable effects.

With regard to the *relative frequency of reporting* of adverse reactions during post marketing surveillance, the undesirable effects at the gastrointestinal level were those received most frequently by the MAH (approximately 45% of all case reports in the company safety database) followed by cutaneous/hypersensitivity-type reactions, which is in agreement with the known side effects profile of the NSAIDs drug class.

Description of selected adverse reactions

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 special precautions for use).

4.9 Overdose

The toxic dose of DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS has not been determined and there is minimal experience of overdosage. Intensification of the pharmacological effects may occur with overdosage.

Symptoms

Clinical signs that may indicate diclofenac overdose include gastrointestinal complaints, confusion, drowsiness, headache, dizziness, disorientation, excitation, coma, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible. Clinical signs that may indicate misoprostol overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension, or bradycardia.

Management

Patients should be managed by symptomatic and supportive care following an overdose of DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS. There are no specific antidotes. The use of activated charcoal, as first line treatment, may help reduce the absorption of DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS. In the case of overdose, renal function should be monitored. Special measures such as haemodialysis or haemoperfusion are unlikely to be helpful in accelerating the elimination of diclofenac and misoprostol, due to the high protein binding and extensive metabolism.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids (ATC code): M01AB55

DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS is a non-steroidal, anti-inflammatory drug, which is effective in treating the signs and symptoms of arthritic conditions.

This activity is due to the presence of diclofenac, which has been shown to have anti-inflammatory and analgesic properties.

DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS also contains the gastroduodenal mucosal protective component misoprostol, which is a synthetic prostaglandin E_1 analogue that enhances several of the factors that maintain gastroduodenal mucosal integrity.

DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS administered twice a day (bd) provides 200 micrograms less misoprostol than thrice daily (tds), whilst providing the same daily dose (150 mg) of diclofenac and may offer a better therapeutic ratio for certain patients.

5.2 Pharmacokinetic properties

The pharmacokinetic profiles following oral administration of a single dose or multiple doses of diclofenac sodium and misoprostol administered as DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS are similar to the profiles when the two drugs are administered as separate tablets. There are no pharmacokinetic interactions between the two components, apart from a slight decrease in diclofenac sodium Cmax when administered concomitantly with misoprostol.

Diclofenac sodium is completely absorbed from the gastrointestinal (GI) tract after fasting oral administration. Only 50 % of the absorbed dose is systemically available due to first-pass metabolism. Peak plasma levels are achieved in 2 hours (range 1-4 hours), when given as a single-dose under fasting conditions. Under fed conditions diclofenac Tmax is increased to 4 hours. The area-under-the plasma-concentration curve (AUC) is dose proportional within the range of 25 mg to 150 mg. The steady state absorption of diclofenac is reduced following the administration of DICLOFENAC

SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS tablets with food, Cmax and AUC are reduced by approximately 40% and 20%, respectively.

The terminal half-life is approximately 2 hours. Clearance and volume of distribution are about 350 ml/min and 550 ml/kg, respectively. More than 99 % of diclofenac sodium is reversibly bound to human plasma albumin, and this has been shown not to be age dependent. Diclofenac metabolism is predominantly mediated via cytochrome P450 CYP2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered diclofenac with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Diclofenac sodium is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65 % of the dose is excreted in the urine and 35 % in the bile. Less than 1 % of the parent drug is excreted unchanged.

Misoprostol is rapidly and extensively absorbed, and it undergoes rapid metabolism to its active metabolite, misoprostol acid, which is eliminated with an elimination $t_{½}$ of about 30 minutes. No accumulation of misoprostol acid was found in multiple-dose studies, and plasma steady state was achieved within 2 days. The serum protein binding of misoprostol acid is less than 90 %. Approximately 73 % of the administered dose is excreted in the urine, mainly as biologically inactive metabolites. In patients with mild-to-moderate renal impairment, $t_{1/2}$ (elimination half-life), C_{max}, and AUC were increased compared to controls, but there was no clear correlation between the degree of renal impairment and AUC. In patients with total renal failure, AUC was approximately doubled in four of six patients.

Single and multiple-dose studies have been conducted comparing the pharmacokinetics of DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS with the diclofenac 75 mg and misoprostol 200 micrograms components administered separately. Bioequivalence between the two methods of providing diclofenac were demonstrable for AUC and absorption rate (C_{max}/AUC). In the steady state comparisons under fasted conditions bioequivalence was demonstrable in terms of AUC. Food reduced the rate and extent of absorption of diclofenac for both DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS and co-administered diclofenac. Despite the virtually identical mean AUCs in the fed, steady state, statistical bioequivalence was not established. This however is due to the broad co-efficients of variation in these studies due to the wide inter-individual variability in time to absorption and the extensive first-pass metabolism that occurs with diclofenac.

Bioequivalence in terms of AUC (0-24 h) was demonstrable when comparing steady state pharmacokinetics of DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS given bd with diclofenac 50 mg/misoprostol 200 micrograms given tds, both regimens providing a total daily dose of 150 mg diclofenac.

With respect to administration of misoprostol, bioequivalence was demonstrated after a single dose of DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS or misoprostol administered alone. Under steady state conditions food decreases the misoprostol C_{max} after DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS administration and slightly delays absorption, but the AUC is equivalent.

5.3 Preclinical safety data

In co-administration studies in animals, the addition of misoprostol did not enhance the toxic effects of diclofenac. The combination was also shown not to be teratogenic or mutagenic. The individual components show no evidence of carcinogenic potential.

Misoprostol in multiples of the recommended therapeutic dose in animals has produced gastric mucosal hyperplasia. This characteristic response to E-series prostaglandins reverts to normal on discontinuation of the compound.

6. Pharmaceutical particulars

6.1 List of excipients

DICLOFENAC SODIUM 75 MG & MISOPROSTOL 200 MCG TABLETS tablets contain:

Microcrystalline cellulose

Maize starch

Sodium benzoate

Purified Talc

Magnesium stearate

Sodium starch glycolate

Colloidal silicon dioxide

Croscarmellose sodium

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package.

6.5 Nature and contents of container

10x10 Alu-Alu Blister.

(10 Tablets are packed in Alu-Alu blister & such 10 blisters are packed in a carton alongwith pack insert).

7. Manufacturer

Health Care Formulations Pvt Ltd.
C/8, Sardar Estate, Ajwa Road,
Vadodara, 390 019, INDIA.