SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Misofen 50mg/200microgram modified release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet consists of a gastro-resistant core containing 50 mg diclofenac sodium surrounded by an outer mantle containing 200 micrograms misoprostol.

Excipient with known effect:

Each tablet contains 20.0 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified Release Tablet

White circular, biconvex uncoated tablets plain one side and embossed with “DM2” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Misofen tablets are indicated for patients who require the non-steroidal anti-inflammatory drug diclofenac together with misoprostol.

The diclofenac component of Misofen Tablets is indicated for the symptomatic treatment of osteoarthritis and rheumatoid arthritis. The misoprostol component of Misofen 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

Adults

One tablet to be taken with food, two or three times daily. Tablets should be swallowed whole, not chewed.

Elderly/Renal 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 or hepatic impairment should be closely monitored (see section 4.4 and section 4.8).

Paediatric population (under 18 years)

The safety and efficacy of Misofen Tablets in children has not been established.

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

4.3 Contraindications

Hypersensitivity to the active substance) or to any of the excipients listed in section 6.1.

Misofen Tablets are 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,

-In 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,

- Patients with established congestive heart failure (NYHA II-IV), ischemic 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.

Use in women of childbearing potential (see also section 4.3)

Misofen 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, Misofen 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 postmarketing 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 pre-treatment state upon discontinuation of NSAID therapy. Patients at greatest risk of such a reaction are those with congestive heart failure, liver cirrhosis, nephrotic syndrome and 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 (eg. 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 Misofen, 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).

Misofen 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, and generalised bullous fixed drug eruption have been reported very rarely in association with the use of diclofenac (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.

• Misofen Tablets may mask fever and thus an underlying infection.

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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 can 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 Arthrotec 75 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/Misoprostol Tablets with anti-coagulants. NSAIDs may enhance the effects of anti-coagulants, such as warfarin, antiplatelet agents, such as aspirin, and serotonin re-uptake inhibitors (SSRIs) thereby increasing the risk of gastrointestinal bleeding (see section 4.4). Close monitoring of such patients is therefore recommended.

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 side effects generally.

Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors and 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

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.

Women of childbearing potential

Women of childbearing potential must be informed about the risk of teratogenicity prior to treatment with Misofen. 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

Misofen Tablets are 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 sucking 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 a 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.

From the 20th week of pregnancy onward, Misofen Tablets use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is 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. Therefore, during the first and second trimester of pregnancy, Misofen Tablets should not be given unless clearly necessary. If Misofen Tablets 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 and ductus arteriosus constriction should be considered after exposure to Misofen Tablets for several days from gestational week 20 week onward. Misofen Tablets should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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.

Consequently, Misofen Tablets is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3)

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. Misofen Tablets should therefore not be administered to nursing mothers.

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.

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 diclofenac/misoprostol was administered to more than 2000 patients are listed. Additionally, adverse drug reactions have been identified during post-marketing surveillance 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 (1564 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.

Organ System	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)	Frequency: Unknown (Post-marketing experience)
Infections and infestations			Vaginal infection			
Blood and lymphatic system disorders			Thrombo-cytopaenia leucopenia			Aplastic anaemia, agranulocytosis, haemolytic anaemia, platelet

						aggregation inhibition
Immune system disorders			Hypersensitivity	Anaphylactic reaction		
Metabolism and nutrition disorders			Decreased appetite			Fluid retention
Psychiatric disorders		Insomnia	Depression, anxiety	Nightmares		Psychotic disorder, disorientation, mood change, irritability
Nervous system disorders		Headache, dizziness	Cerebrovascular accident, somnolence , tremor, Paraesthesia			Meningitis aseptic1, convulsion, memory impairment, dysgeusia
Eyes disorders			Vision blurred			Visual impairment
Ear and labyrinth disorders			Tinnitus			
Cardiac disorders			Cardiac failure, myocardial Infarction palpitations ,			Kounis syndrome
Vascular disorders			hypertension	hypotension		Shock, vasculitis
Respiratory, thoracic and mediastinal disorders			dyspnoea	pneumonitis		Asthma,
Gastrointes	Abdom	Gastritis,	Stomatitis	Pancreati		Gastrointestin

tinal disorders	inal pain, diarrhoea[2] , nausea, dyspepsia	vomiting, flatulence, eructation, constipation, peptic ulcer gastrointestinal inflammation, gastrointestinal ulcer, duodenitis, oesophagitis	melaena, mouth ulceration, dry mouth, gastrointestinal bleeding3	tis, haematemesis, colitis, oesophageal disorder, glossitis		al perforation[3], Crohn's disease, tongue oedema
Hepato-biliary 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 Schönlein purpura, mucocutaneous rash, rash vesicular, DRESS syndrome Fixed drug eruption Generalised bullous fixed drug eruption
Renal and urinary disorders						Renal failure, acute renal failure, renal papillary necrosis, tubulointerstit

						ial Nephritis nephrotic syndrome, proteinuria, haematuria, glomerulonephritis, glomerulonephritis minimal lesion, glomerulonephritis membranous, renal impairment
Pregnancy, puerperium and perinatal conditions						Foetal death, incomplete abortion, 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, dysmenorrhea		Uterine haemorrhage uterine spasm, infertility (female fertility decreased)
Congenital, familial and genetic disorders		Foetal malformation				

General disorders and administration site conditions			Oedema[5] , chest pain, face oedema, fatigue, pyrexia, chills			inflammation
Investigations		Alanine aminotransferase increased, blood alkaline phosphatase increased, haematocrit decreased	Blood bilirubim increased, aspartate aminotransf erase increased			
Injury, poisoning and procedural complications						Uterine perforation Uterine rupture,

[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 Misofen 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 section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

Reporting 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The toxic dose of Misofen Tablets has not been determined and there isminimal 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

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures. It is reasonable to take measures to reduce absorption of any recently consumed drug by forced emesis, gastric lavage or activated charcoal.

Induced diuresis may be beneficial because diclofenac and misoprostol metabolites are excreted in the urine, provided that the patient does not develop renal failure at diclofenac overdose. Special measures such as haemodialysis or haemoperfusion are probably 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,

ATC code: M01BX

Misofen Tablet is a non-steroidal, anti-inflammatory drug, which is effective in treating the signs and symptoms of arthritic conditions.

Mechanism of action

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

Misofen Tablets also contain the gastroduodenal mucosal protective component misoprostol, which is a synthetic prostaglandin E1 analogue that enhances several of the factors that maintain gastroduodenal mucosal integrity.

5.2 Pharmacokinetic properties

The pharmacokinetic profiles following oral administration of a single dose or multiple doses of diclofenac sodium and misoprostol administered as Misofen Tablets are similar to the profiles when the two drugs are administered as separate tablets. There are no pharmacokinetic interactions between the two components.

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), and the area-under-the plasma-concentration curve (AUC) is dose proportional within the range of 25 mg to 150 mg. The extent of diclofenac sodium absorption is not significantly affected by food intake.

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 t½ 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, $t_{1/2}$, 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.

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

Core:

lactose monohydrate

microcrystalline cellulose

maize starch

povidone K-30

magnesium stearate

purified talc

Mantle/Coat:

hypromellose

methylacrylic acid copolymer type C

purified talc

triethylcitrate

sodium starch glycolate

hydrogenated castor oil

microcrystalline cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicine product does not require any special storage instructions.

6.5 Nature and contents of container

Misofen Tablets are presented in packs composed of OPA-ALU-PVC blisters with aluminium foil.

Pack size: 7, 10, 14, 15, 20, 28, 30, 50, 60, 90, 100, 140 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:

Morningside Healthcare Limited

115 Narborough Road

Leicester, LE3 0PA

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0187

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/10/2012

10 DATE OF REVISION OF THE TEXT

11/09/2025