1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

MISOPROSTOL AND DICLOFENAC SODIUM TABLETS (ZYTROTEC)

2. Qualitative and quantitative composition

SR. NO.	NAME OF THE INGREDIENTS	PHARMACOPEIL SPECIFICATION	LABLE CLAIM	OVERAGES %	QTY. / TABLET	PURPOSE
ACTIVE INGREDIENTS						
1.	Misoprostol (1% HPMC Dispersion)	USP	200 mcg	0.00%	20.000 mg	API
2.	Diclofenac sodium (As Enteric Coated)	USP	75 mg	0.00%	75.000 mg	API
INACTIVE INGREDIENTS						
3.	Dibasic calcium phosphate	BP	-	0.00%	335.000 mg	Diluent
4.	Cellulose acetate Phthalate	BP	-	0.00%	55.000 mg	Binder
5.	Povidone	BP	-	0.00%	16.500 mg	Binder
6.	Isopropyl alcohol*	BP	-	0.00%	0.400 ml	Solvent
7.	Magnesium stearate	BP	-	0.00%	5.500 mg	Lubricant
8.	Purified talc	BP	-	0.00%	11.000 mg	Glidant
9.	Croscarmellose sodium	BP	-	0.00%	16.500 mg	Disintegrant
10.	Colloidal silicon Dioxide	USP	-	0.00%	5.500 mg	Glidant
11.	Hydroxy propyl methyl cellulose (E-15)	BP	-	0.00%	4.900 mg	Polymer
12.	Purified talc	BP	-	0.00%	0.350 mg	Polisher
13.	Polyethylene glycol (Macrogols 6000)	BP	-	0.00%	1.400 mg	Plasticizer
14.	Titanium dioxide	BP	-	0.00%	0.350 mg	Opacifier
15.	Dichloromethane*	BP	-	0.00%	0.800 ml	Solvent
16.	Isopropyl alcohol*	BP	-	0.00%	0.600 ml	Solvent
17.	Yellow oxide of Iron	INHOUSE	-	0.00%	3.000 mg	Colour

*** Evaporates during manufacturing & does not remain in final product.

3. Pharmaceutical form

Oral tablet

4. Clinical particulars

4.1 Therapeutic indications

Misoprostol and Diclofenac Sodium Tablets are indicated for patients who require the non-steroidal anti-inflammatory drug diclofenac together with misoprostol.
The diclofenac component of Misoprostol and Diclofenac Sodium Tablets is indicated for the symptomatic treatment of osteoarthritis and rheumatoid arthritis. The misoprostol component of Misoprostol and Diclofenac Sodium 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.
Adults
One tablet to be taken with food, two times daily. Tablets should be swallowed whole, not chewed.
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.
Paediatric population
The safety and efficacy of Misoprostol and Diclofenac Sodium Tablets in children under 18 years has not been established.

4.3 Contraindications

Misoprostol and Diclofenac Sodium 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.
- 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), 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 NSAID may increase frequency of gastrointestinal ulcers and bleeding.
Use in pre-menopausal women: Misoprostol and Diclofenac Sodium Tablets should not be used in pre-menopausal women unless they use effective contraception and have been advised of the risks of taking the product if pregnant.
Precautions:
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Cardio vascular risk: NSAIDs may cause an increased risk of serious CV thrombotic events, MI, and stroke, which can be fatal. This risk may increase with length of therapy. Patients with CV disease or risk factors for CV disease may be at greater risk. Diclofenac / misoprostol are contraindicated for treatment of perioperative pain in the setting of CABG surgery.
Gastro Intestinal risk: NSAIDs cause an increased risk of serious GI adverse reactions, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These reactions can occur at any time during use, with or without warning symptoms. Elderly patients are at greater risk of serious GI events.
Skin reactions: 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/misoprostol. 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.
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.

- Misoprostol and Diclofenac Sodium Tablets may mask fever and thus an underlying infection.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

- NSAIDs may attenuate the natriuretic efficacy of diuretics due to inhibition of intra renal 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 cyclosporine. When co-administered with cyclosporine, there is a two-fold increase in diclofenac systemic exposure. It is prudent to start with the lowest dose of Misoprostol and Diclofenac Sodium 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.
- Because of decreased platelet aggregation caution is advised when using Misoprostol and Diclofenac Sodium Tablets with anti-coagulants. NSAIDs may enhance the effects of anti-coagulants, such as warfarin, antiplatelet agents, such as acetylsalicylic acid, and serotonin re-uptake inhibitors (SSRIs) thereby increasing the risk of gastrointestinal bleeding.
- 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 Pregnancy and lactation

Pregnancy:
Misoprostol and Diclofenac Sodium Tablets is contraindicated in pregnant women and in women planning a pregnancy because misoprostol induces uterine contractions and is associated with abortion, premature birth, and fetal death. Use of misoprostol has been associated with birth defects. Also diclofenac may cause premature closure of the ductus arteriosus.
Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.
Women of childbearing potential should not be started on diclofenac/misoprostol until pregnancy is excluded, and should be fully counseled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, use of the product should be discontinued.
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. Misoprostol and Diclofenac Sodium 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/misoprostal, 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.

4.8 Undesirable effects

Adverse drug reactions reported during post-marketing surviellance are whose frequency cannot be estimated from the available data, such as spontaneous reports, have been listed at frequency 'unknown'. 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.
Infections and infestations: Uncommon: Vaginal infection, Unknown: Aseptic meningitis
Blood and lymphatic system disorders: Uncommon: Thrombo-cytopenia, Unknown: Aplastic anaemia, agranulocytosis, haemolytic anaemia, leucopenia, platelet aggregation inhibition
Immune system disorders: Rare: Anaphylactic reaction, Unknown: Hypersensitivity
Metabolism and nutrition disorders: Unknown: Anorexia, fluid retention
Psychiatric disorders: Common: Insomnia, Very Rare: Nightmares, Unknown: Psychotic reaction, disorientation, depression, anxiety, mood change, irritability

Nervous system disorders: Common: Headache, dizziness, Uncommon: Cerebrovascular accident, Unknown: Convulsions, memory disturbance, drowsiness, tremor, taste disturbance, paraesthesia
Cardiac disorders: Uncommon: Myocardial infarction
Vascular disorders: Uncommon: Hypertension
Gastrointestinal disorders: Very Common: Abdominal pain, diarrhoea, nausea, dyspepsia, Common: Gastritis, vomiting, flatulence, eructation, constipation, peptic ulcer, gastrointestinal inflammation, duodenitis, oesophagitis, Uncommon: Stomatitis, gastrointestinal bleeding, Rare: Pancreatitis
Skin and subcutaneous tissue disorders: Common: Rash, pruritus, Uncommon: Purpura, urticarial, Rare: Angioedema, Very Rare: Dermatitis bullous
Reproductive system and breast disorders: Uncommon: Menorrhagia, metrorrhagia, vaginal haemorrhage, postmenopausal haemorrhage, menstrual disorder, Rare: Breast pain, dysmenorrhea.

4.9 Overdose

The toxic dose of Misoprostol and Diclofenac Sodium Tablets has not been determined and there is no experience of overdosage. Intensification of the pharmacological effects may occur with overdose.
Symptoms:
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

Misoprostol and Diclofenac Sodium 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.
Misoprostol and Diclofenac Sodium Tablets also contain the gastro duodenal mucosal protective component misoprostol, which is a synthetic prostaglandin E_1 analogue that enhances several of the factors that maintain gastro duodenal mucosal integrity.
Misoprostol and Diclofenac Sodium Tablets administered bd provides 200 micrograms less misoprostol than Misoprostol and Diclofenac Sodium Tablets 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 Misoprostol and Diclofenac Sodium Tablets are similar to the profiles when the two drugs are administered as separate tablets.
Misoprostol: Misoprostol is rapidly absorbed following oral administration, with peak plasma levels of the active metabolite (misoprostol acid) occurring after about 30 minutes. The plasma elimination half-life of misoprostol acid is 20-40 minutes. No accumulation of misoprostol acid in plasma occurs after repeated dosing of 400 micrograms twice daily.
Diclofenac Sodium: Diclofenac sodium is rapidly absorbed from the gut and is subject to first-pass metabolism. Therapeutic plasma concentrations occur about ½ hour after administration of Diclofenac Sodium. The active substance is 99.7% protein bound and the plasma half-life for the terminal elimination phase is 1-2 hours. Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. The remainder of the dose is excreted via the bile in metabolised form.

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

- Dibasic calcium phosphate
- Cellulose acetate phthalate
- Povidone
- Isopropyl alcohol
- Magnesium stearate
- Purified talc
- Croscarmellose sodium
- Colloidal silicone dioxide
- Hydroxy propylmethyl cellulose (E-15)
- Polyethylene glycol (Macrogols 6000)
- Titanium dioxide
- Dichloromethane
- Yellow oxide of iron

6.2 Incompatibilities

None known

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a dry place at a temperature below 30°C

6.5 Nature and contents of container

10 X 10 Tablets Alu- Alu pack, packed in printed and laminated carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

West Coast Pharmaceutical Works Ltd, Ahmedabad

8. Marketing authorisation number(s)

Not applicable.

9. Date of first authorisation/renewal of the authorisation

Not applicable.

10. Date of revision of the text

September, 2021