SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OSTEOTEC (Diclofenac Sodium and Misoprostol Delayed Release Tablets 75 mg/0.2 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Diclofenac Sodium and Misoprostol 75 mg/0.2 mg delayed-release tablet contains 75 mg diclofenac sodium and 0.2 mg misoprostol.

Excipient with known effect:

Each Diclofenac Sodium and Misoprostol 75 mg/0.2 mg delayed-release tablet contains 5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Delayed Release Tablets

White to off white coloured round shaped biconvex uncoated tablet plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diclofenac sodium and misoprostol delayed-release tablets are indicated for treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications. For a list of factors that may increase the risk of NSAID-induced gastric and duodenal ulcers and their complications.

4.2 Posology and method of administration

Adults

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

Elderly and patients with renal, cardiac or 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.

Children (under 18 years)

The safety and efficacy of diclofenac/misoprostol 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.

Route of Administration: Oral

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Patients with active peptic ulcer/haemorrhage or perforation or who have active gastrointestinal (GI) bleeding or other active bleedings e.g. cerebrovascular bleedings.
- Patients who previously suffered from gastro-intestinal bleeding caused by NSAIDs.
- Pregnant women and in women planning a pregnancy.
- Breastfeeding women
- Patients with a known hypersensitivity to aspirin, other NSAIDs, or other prostaglandins.
- Patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin 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.

4.4 Special warnings and precautions for use

Warnings

The use of diclofenac/misoprostol with concomitant NSAIDs including COX-2 inhibitors should be avoided.

Use in pre-menopausal women

Diclofenac/misoprostol 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. The label will state: ‘Not for use by pre-menopausal women unless using effective contraception’.

Precautions

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Renal, cardiac or 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/misoprostol should be used only in exceptional circumstances and with close clinical monitoring: advanced cardiac failure, advanced kidney failure, 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. 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 and overt renal disease. Such patients should be carefully monitored while receiving NSAID therapy.

Appropriate monitoring and advice are required for patients with a history of hypertension 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 (150 mg 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.
<u>Blood system/Gastrointestinal</u>
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 aspirin, 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.

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, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin.

Diclofenac/misoprostol, 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.

Care should be taken in elderly patients and in patients treated with corticosteroids, other NSAIDs, or anti-coagulants.

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.

Diclofenac/misoprostol 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 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, cyclo-oxygenase inhibitors such as diclofenac can increase the nephrotoxicity of ciclosporin. 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 also advised when using diclofenac/misoprostol 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.

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.

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 and angiotensin II antagonists (AIIA): NSAIDs can reduce the efficacy of diuretics and other antihypertensive drugs.

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 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Diclofenac/misoprostol is contraindicated in pregnant women and in women planning a pregnancy because misoprostol induces uterine contractions and is associated with abortion, premature birth, and foetal death. Use of misoprostol has been associated with birth defects. Also diclofenac may cause premature closure of the ductus arteriosus.

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.

Breastfeeding

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/misoprostol should therefore not be administered to nursing mothers.

Fertility

No fertility data are available.

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

Most common adverse reactions (>2%) are: abdominal pain, diarrhea, dyspepsia, nausea, flatulence, gastritis, vomiting, constipation, headache, dizziness, alanine aminotransferase increased, hematocrit decreased.

4.9 Overdose

The toxic dose of diclofenac/misoprostol has not been determined and there is no experience of overdosage. Intensification of the pharmacological effects may occur with overdosage. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory/antirheumatic agents in combination.

ATC code: M01BX

Mechanism of action:

Diclofenac sodium and misoprostol tablets are a combination product containing diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties, and misoprostol, a GI mucosal protective prostaglandin-1 (PGE1) analog.

Diclofenac

The mechanism of action of diclofenac, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Diclofenac is a potent inhibitor of prostaglandin (PG) synthesis in vitro. Diclofenac concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because diclofenac is an inhibitor of

prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Misoprostol

Misoprostol is a synthetic PGE1 analog with gastric antisecretory and mucosal protective properties. NSAIDs inhibit prostaglandin synthesis. A deficiency of prostaglandins within the gastric and duodenal mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by NSAIDs.

Misoprostol can increase bicarbonate and mucus production, but it has been shown at doses 200 mcg and above that are also antisecretory. It is therefore not possible to differentiate whether the ability of misoprostol to reduce the risk of gastric and duodenal ulcers is the result of its antisecretory effect, its mucosal protective effect, or both.

In vitro studies on canine parietal cells using titrated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors.

Receptor binding is saturable, reversible, and stereo-specific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine.

Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol, over the range of 50 mcg to 200 mcg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 mcg were modest and shorter-lived, and only the 200 mcg dose had substantial effects on nocturnal secretion or on histamine- and meal-stimulated secretion.

Misoprostol also produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor intrinsic factor output.

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/misoprostol 50 mg/200 microgram and diclofenac sodium/misoprostol 75 mg/200 microgram are similar to the profiles when the two drugs are administered as separate tablets and 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/misoprostol 75 mg/200 microgram 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 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 70% of the administered dose is excreted in the urine, mainly as biologically inactive metabolites.

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

Lactose Monohydrate (200#)

Microcrystalline Cellulose PH 102

Povidone K-30

Purified Water

Crospovidone XL 10

Pregelatinized Maize Starch (Starch 1500)

Magnesium Stearate

Hypromellose 6cps

Polyethylene glycol 400

Isopropyl Alcohol

Dichloromethane

Sheffcoat ENT MA Brown 5Y02081

Colloidal Silicon Dioxide

Hydrogenated Castor Oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blisters packs (aluminium) with 10 and 100 delayed-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

Manufactured by:

Celogen Pharma Pvt. Ltd.

B-106, Techno City, X-4/1, TTC Ind. Area,

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Marketed by:

BOCHE PHARM NIG LTD

Yaba - Lagos, Nigeria.

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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