SUMMARY OF PRODUCT CHARACTERISTIC (SMPC)

1. Name of the Medicinal Product

Misoprostol Tablets 200 mcg (ACE MISO)

2. Qualitative and Quantitative Composition

Each Uncoated tablet contains:

Misoprostol EP..... 200 mcg

Excipients… ..... q.s.

3. Pharmaceutical Form

White to off white, round, biconvex, uncoated tablets, plain on both sides.

4. Clinical Particulars

4.1 Therapeutic indications

ACE MISO is indicated for Prevention & Treatment of postpartum hemorrhage.

4.2 Posology and method of administration

For prevention of postpartum haemorrhage - 600µg of misoprostol (3 X 200 µg of ACE MISO) should give orally immediately after cord clamping.

Renal Impairment

No routine dosage adjustment is recommended in patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.

Hepatic Impairment

Misoprostol is metabolised by fatty acid oxidising systems present in organs throughout the body. Its metabolism and plasma levels are therefore unlikely to be affected markedly in patients with hepatic impairment.

4.3 Contraindications

Administration of ACE MISO is contraindicated in patients with any one of the following conditions:

- Known hypersensitivity to misoprostol or other prostaglandins.
- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy);

- Chronic adrenal failure;
- Heamorrhagic disorders or concurrent anticoagulant therapy;
- Inherited prophyria

4.4 Special warnings and precautions for use

General:

THE PATIENT SHOULD NOT GIVE ACE MISO TO ANYONE ELSE.

- ACE MISO has been prescribed for the patient's specific condition, may not be the the correct treatment for another person, and may be dangerous to the other person if she is or were to become pregnant.
- Misoprostol should be used with caution in patients with conditions that predispose them to diarrhoea, such as inflammatory bowel disease. To minimise the risk of diarrhoea, misoprostol should be taken with food, and magnesium containing antacids should be avoided.
- Misoprostol should be used with caution in patients in whom diarrhea leading to severe dehydration would be dangerous. These patients should be monitored carefully.

During the period immediately following the administration of Misoprostol, the patient may need medication for cramps or gastrointestinal symptoms. The patient should be given instructions on what to do if significant discomfort, excessive bleeding other adverse reactions occur and should be given a phone number to call if she has questions following the administration of the ACE MISO.

ACE MISO should be administerd orally immediately after cord clamping.

Misoprostol should be used with caution in the presence of disease states where hypotension might precipitate severe complications, e.g. cerebrovascular disease, coronary artery disease or severe peripheral vascular disease including hypertension.

4.5 Interactions with other medicinal products and other forms of interaction

Concomitant administration of NSAIDs and misoprostol in rare cases can cause a transaminase increase and peripheral oedema.
Misoprostol is predominantly metabolised via fatty acid oxidising systems and has shown no adverse effect on the hepatic microsomal mixed function oxidase (P450) enzyme system. In specific studies no clinically significant pharmacokinetic interaction has been

demonstrated with antipyrine or diazepam. A modest increase in propranolol concentrations (mean approximately 20% in AUC, 30% in Cmax) has been observed with multiple dosing of misoprostol. In extensive clinical studies no drug interactions have been attributed to Misoprostol. Drug interaction studies with misoprostol and several NSAIDs showed no clinically significant effect on the kinetics of ibuprofen, diclofenac, piroxicam, aspirin, naproxen or indomethacin. Magnesium containing antacids should be avoided during treatment with misoprostol as this may worsen the misoprostol induced diarrhoea.

4.6 Fertility, pregnancy and lactation

Pregnancy

ACE MISO is contraindicated in women who are pregnant because it induces uterine contractions and is associated with abortion, premature birth, foetal death and birth defects. First trimester exposure to misoprostol is associated with a significantly increased risk of two birth defects: Möbius sequence (i.e. palsies of cranial nerves VI and VII) and terminal transverse limb defects. Other defects including arthrogryposis have been observed.

The risk of uterine rupture increases with advancing gestational age and with prior uterine surgery, including Caesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.

Lactation

Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and excreted in the breast milk. ACE MISO should not be administered to nursing mothers because of the potential excretion of misoprostol acid could cause undesirable effects such as diarrohoea in nursing infants.

4.7 Effects on ability to drive and use machines

ACE MISO can cause dizziness. Patients should be cautioned about operating machinary and driving.

4.8 Undesirable effects

General

- Gastro-intestinal side effects like diarrhoea, abdominal pain, nausea, flatulence, dyspepsia, vomiting and constipation.
- Headache
- Shivering
- Hyperthermia

- Dizziness

Incidence greater than 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving Misoprostol and may be casually related to the drug. Nausea (3.2%), flatulence (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%) and constipation(1.1%). However there were no significant differences between the incidences of these events for Misoprostol and Placebo.

Casual relationship unknown

The following adverse events were infrequently reported. Casual relationships between Misoprostol and these events have not been established but cannot be excluded.

- Body as whole: aches/pains, asthenia, fatigue, fever, rigors, weight changes.
- Skin: rash, dermatitis, alopecia,pallor, breast pain.
- Special senses: abnormal taste, abnormal vision, conjuctivitis, deafness, tinnitus, earache.
- Respiratory: upper respiratory tract infection, bronchitis, brochospasm,dyspnea, pneumonia, epistaxis.
- Cardiovascular: chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope.
- Gastrointestinal: GI bleeding, GI inflammation/infection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux , dysphagia, amylase increase
- Hypersensitivity: anaphylaxis.
- Metabolic: glycosuria, gout, increased nitrogen, increased alkaline phosphatase.
- Genitourinary: polyuria, dysuria, haematuria, urinary tract infection.
- Nervous system/Psychiatric: anxiety, change in appetite, depression, drowsiness, dizziness, thirst, impotence, loss of libido, sweating increase, neuropathy, neurosis, confusion.
- Musculoskeletal: arthralgia, myalgia, muscle cramps, stiffness, back pain.
- Blood/Coagulation: anemia, abnormal differential, thrombocytopenia, purpura, ESR increased.

During Misoprostol use in Obstetrics and Gynaecology use patient may experience pain due to uterine contractions, there may be severe genital bleeding that may lead to Shock. The patient can complain of Pelvic pain. There is a possibility of even Uterine rupture which might require surgical repair, hysterectomy, and/or salpingooophorectomy.

4.9 Overdose

Clinical signs that may indicate an overdosage are sedation, tremor, convulsions, dyspnea, abdomial pain, diarrhea, fever, palpitations, hypotension, or bradycardia. Symptoms should be treated with supportive therapy. It is not known if Misoprostol acid

dialyzable. However, because Misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropiate treatment for over-dosage.

Treatment of Overdose

In cases of overdose, standard supportive measures should be adopted as required. In clinical trials, patients have tolerated 1200 micrograms daily for three months without significant adverse effects.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Misoprostol is a synthetic prostaglandin E1,

ATC code: A02BB01

Mechanism of action

Prostaglandin E1 causes myometrial contractions by interacting with specific receptors on myometrial cells. This interaction results a change in calcium concentration, thereby initiating muscle contraction. By interacting with prostaglandin receptors, misoprostol causes the cervix to soften and the uterus to contract. Uterine contractions facilitate separation of the placenta from the uterine wall and reduce postpartum haemorrhage.

5.2 Pharmacokinetic properties

Misoprostol is rapidly & extensively absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, metabolite is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give Prostaglandin-F anologs. The compound is a lipophilic methyl ester pro drugs and is readily metabolized to the free acid, which is the biologically active form.

Following oral administration, the plasma misoprostol levels increased rapidly, with a peak at 30 minutes, declined rapidly by 120 minutes, and remained low thereafter.

5.3 Preclinical safety data

In single and repeat-dose studies in dogs, rats and mice at multiples of the human dose, toxicological findings were consistent with the known pharmacological effects of the E-type prostaglandins, the main symptoms being diarrhea, vomiting, mydriasis, tremors and hyperpyrexia. Gastric mucosal hyperplasia was also observed in the mouse, rat and the dog. In the rat and the dog, the hyperplasia was reversible on discontinuation of misoprostol fallowing one year of dosing. Histological examination of gastric biopsies in

humans has shown no adverse tissue response after up to one year's treatment. In studies of fertility, teratogenicity and pre/post-natal toxicity in rats and rabbits there were no major findings. A decrease in implantations and some pup growth retardation was observed at doses greater than 100 times the human dose. It was concluded that misoprostol does not significantly affect fertility, is not teratogenic or embryo toxic and does not affect rat pups in the pre/post-natal period.

Misoprostol was negative in a battery of 6 in-vitro assays and 1 in-vivo test to assess mutagenic potential. In carcinogenicity studies in the rat and mouse it was concluded that there was no risk of carcinogenic hazard.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose

Sodium Starch Glycolate

Hydrogenated Castor Oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30ºC. Protect from light.

6.5 Nature and contents of container

The tablets are packed in cold form aluminium (Alu-Alu) blister of 4 tablets. One blister is packed in an inner carton and then further 10 inner cartons are packed in one outer carton along with package insert.

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

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8. Marketing Authorisation Number(s)

07949/08429/REN/2022

9. Date of first Authorisation/Renewal of the Authorisation

Oct 12, 2022

10. Date of Revision of the Text

24.03.2022