SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

Breeky® **(Misoprostol) 200mcg Tablets**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Breeky® 200mcg Tablets

Each tablet contains:
Misoprostol dispersion USP
equivalent to Misoprostol.....200mcg

3. PHARMACEUTICAL FORM

Tablet

Appearance: Dark pink, round flat with bevel edge tablet, cross line on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Breeky® is indicated for the healing of duodenal ulcer and gastric ulcer including those induced by nonsteroidal anti-inflammatory drugs (NSAID) in arthritic patients at risk, whilst continuing their NSAID therapy. In addition, **Breeky®** can be used for the prophylaxis of NSAID-induced ulcers.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:
Adults: ***Healing of duodenal ulcer, gastric ulcer and NSAID-induced peptic ulcer:*** 800mcg daily in two or four divided doses taken with breakfast and / or each main meal and at bedtime. Treatment should be given initially for at least 4 weeks even if symptomatic relief has been achieved sooner. In most patients' ulcers will be healed in 4 weeks but treatment may be continued for up to 8 weeks if required. If the ulcer relapses further treatment courses may be given. ***Prophylaxis of NSAID-induced peptic ulcer:*** 200mcg twice daily, three times daily or four times daily. Treatment can be continued as required. Dosage should be individualised according to the clinical condition of each patient. ***Renal impairment:*** Available evidence indicates that no adjustment of dosage is necessary in patients with renal impairment. ***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.
Elderly: The usual dosage may be used.
Paediatric population: Use of Misoprostol in children has not yet been evaluated in the treatment of peptic ulceration or NSAID-induced peptic ulcer disease.
Method of administration:
For oral use.

4.3. CONTRAINDICATIONS:

Misoprostol is contraindicated:
- In women of childbearing potential who are not using effective contraception.
- In women who are pregnant, or in whom pregnancy has not been excluded, or who are planning a pregnancy as misoprostol increases uterine tone and contractions in pregnancy which may cause partial or complete expulsion of the products of conception. Use in pregnancy has been associated with birth defects.
- In patients with a known hypersensitivity to misoprostol or to any excipient of the product, or to other prostaglandins.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

In women of childbearing potential Misoprostol must not be started on misoprostol until pregnancy is excluded, and should be fully counselled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, use of the product should be discontinued. In such patients it is advised that Misoprostol should only be used if the patient:
- takes effective contraceptive measures
- has been advised of the risks of taking Misoprostol if pregnant

Gastrointestinal bleeding, ulceration, and perforation have occurred in NSAID-treated patients receiving misoprostol. Physicians and patients should remain alert for ulceration, even in the absence of gastrointestinal symptoms, and, where appropriate, endoscopy and biopsy should be carried out before use to ensure that malignant disease is absent in the upper gastrointestinal tract. These investigations and any others considered necessary by the clinician should be repeated at appropriate intervals for follow-up purposes. Symptomatic responses to misoprostol do not preclude the presence of gastric malignancy. Misoprostol should be used with caution in patients with conditions that predispose them to diarrhoea, such as inflammatory bowel disease. To minimize 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 dehydration would be dangerous. These patients should be monitored carefully. The results of clinical studies indicate that Misoprostol does not produce hypotension at dosages effective in promoting the healing of gastric and duodenal ulcers. Nevertheless, 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. There is no evidence that Misoprostol has adverse effects on glucose metabolism in human volunteers or patients with diabetes mellitus. **Breeky®** contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium free'.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

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 C_{max}) 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:

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

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.
Breast-feeding: Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. Misoprostol should not be administered to nursing mothers because the excretion of misoprostol acid could cause undesirable effects such as diarrhoea in nursing infants.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Misoprostol can cause dizziness. Patients should be cautioned about operating machinery and driving.

4.8. UNDESIRABLE EFFECTS:

The Adverse reaction terms were then categorised utilising the incidence rate as follows: Very Common: ≥ 1/10 (≥ 10%), Common: ≥ 1/100 and < 1/10, (≥ 1% and <10%), Uncommon: ≥ 1/1000 and < 1/100, (≥ 0.1% and <1%), Rare: ≥ 1/10,000 and < 1/1000, (≥ 0.01% and <0.1%), Very Rare: < 1/10,000, (<0.01%), Not Known.
Immune system disorders: ***Not known:*** Anaphylactic reaction.
Nervous system disorders: ***Common:*** Dizziness, headache.
Gastrointestinal Disorders: ***Very common:*** Diarrhoea. ***Common:*** Abdominal pain, constipation, dyspepsia, flatulence, nausea, vomiting.
Skin and subcutaneous tissue disorders: ***Very common:*** Rash.
Pregnancy, puerperium, and perinatal conditions: ***Rare:*** Uterine rupture. ***Not known:*** Amniotic fluid embolism, abnormal uterine contractions, foetal death, incomplete abortion, premature birth, retained placenta, uterine perforation.
Reproductive System and Breast Disorders: ***Uncommon:*** Vaginal haemorrhage (including postmenopausal bleeding), intermenstrual bleeding, menstrual disorder, uterine cramping. ***Rare:*** Menorrhagia, dysmenorrhoea. ***Not known:*** Uterine haemorrhage.
Congenital, Familial and Genetic Disorders: ***Common:*** Foetal malformations.
General Disorders and Administration Site Conditions: ***Not known:*** Chills. ***Uncommon:*** Pyrexia.

SUMMARY OF PRODUCT CHARACTERISTICS

4.9. OVERDOSE:
Signs and symptoms of overdose: The toxic dose of misoprostol in humans has not been determined. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension, or bradycardia.
Treatment of overdose: Because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage. In cases of overdose, standard supportive measures should be adopted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Prostaglandins, **ATC code:** A02BB01.
Misoprostol is an analogue of naturally occurring prostaglandin E1 which promotes peptic ulcer healing and symptomatic relief.
Mechanism of action: Misoprostol protects the gastroduodenal mucosa by inhibiting basal, stimulated and nocturnal acid secretion and by reducing the volume of gastric secretions, the proteolytic activity of the gastric fluid, and increasing bicarbonate and mucus secretion.

5.2. PHARMACOKINETICS:
Absorption and Distribution: Misoprostol is rapidly absorbed following oral administration, with peak plasma levels of the active metabolite (misoprostol acid) occurring after about 30 minutes.
Biotransformation and Elimination: The plasma elimination half-life of misoprostol acid is 20-40 minutes. No accumulation of misoprostol acid in plasma occurs after repeated dosing of 400mcg twice daily.

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 diarrhoea, 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 following 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 peri/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 embryotoxic and does not affect rat pups in the peri/post-natal period. Misoprostol was negative in a battery of 6 in vitro assays and one 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
- Castor oil hydrogenated
- Erythrosine lake color
- Crospovidone

6.2. INCOMPATIBILITIES:
Not applicable.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Store between 15 to 30°C. Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
Alu/Alu blister, pack size is 10's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
No special requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
Ph. Int. Specs.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

8. MARKETING AUTHORISATION NUMBER(S)

073698

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11th January, 2013

10. DATE OF REVISION OF THE TEXT

بریکی® ۲۰۰ مائیکروگرام ٹیبلٹ
(میسوپروسٹول)

ہدایات:
خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی