Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Name of the medicinal product: PRODOM CAPSULE
Generic name: Enteric Coated Rabeprazole Sodium 20 mg and Sustained

2. Qualitative and quantitative composition

Each hard gelatin capsule contains rabeprazole sodium BP 20 mg (as enteric coated pellets) and domperidone BP 30 mg (as sustained release pellets).
Approved colours are used in the empty capsule shells.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Hard Gelatin capsule.

4. Clinical particulars

4.1 Therapeutic indications

The product is stated to be indicated for the treatment of:

Active duodenal ulcer.
Active benign gastric ulcer.
Symptomatic erosive or ulcerative gastro-oesophageal reflux disease (GORD).
Long-term management of gastro-oesophageal reflux disease (GORD maintenance).
Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD).
Zollinger-Ellison syndrome.
In combination with appropriate antibacterial regimens, for the eradication of Helicobacter pylori in patients with peptic ulcer disease.

4.2 Posology and method of administration

Posology

Adults: Enteric coated Rabeprazole Sodium and Sustained Release Domperidone Capsules up to two times a day or as directed by Physician.

Paediatric population

Enteric coated Rabeprazole Sodium and Sustained Release Domperidone Capsules are not recommended for use in children due to a lack of data on safety and efficacy.

Method of administration

For oral use

4.3 Contraindications

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

Prolactin-releasing pituitary tumour (prolactinoma).
Moderate or severe hepatic impairment.
Co-administration with QT-prolonging medicinal products.
Co-administration with potent CYP3A4 inhibitors.
Pregnancy and breast-feeding.

4.4 Special warnings and precautions for use

Rabeprazole

Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric or oesophageal malignancy; the possibility of malignancy should therefore be excluded prior to commencing treatment. A risk of cross-hypersensitivity reactions with other proton pump inhibitors or substituted benzimidazoles cannot be excluded.

Patients should be cautioned that the capsules should not be chewed or crushed, but should be swallowed whole.

The product is not recommended for use in children due to a lack of data on safety and efficacy.

There have been post-marketing reports of blood dyscrasias (thrombocytopenia and neutropenia). In the majority of cases where an alternative aetiology could not be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole. Co-administration of atazanavir with rabeprazole is not recommended.

Decreased gastric acidity, by any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to a slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

Domperidone

Renal impairment: the elimination half-life of domperidone is prolonged in severe renal impairment.

Cardiovascular effects: domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance there have been very rare cases of QT prolongation and Torsade de Pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.

4.5 Interaction with other medicinal products and other forms of interaction

Rabeprazole

Rabeprazole sodium produces a profound and long-lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur.

Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. Individual patients may therefore need to be monitored to

determine whether a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly.
In clinical trials, antacids were used concomitantly with rabeprazole and, in a specific drug-drug interaction study, no interaction with liquid antacids was observed. Co-administration of atazanavir 300 mg/ritonavir with omeprazole (40 mg once daily), or atazanavir 400 mg with lansoprazole (60 mg once daily), to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with other proton pump inhibitors; rabeprazole should therefore not be co-administered with atazanavir.

Domperidone – concomitant use contraindicated

QTc-prolonging medicinal products, including: class IA antiarrhythmics (e.g. disopyramide, hydroquinidine, quinidine); class III antiarrhythmics (e.g. amiodarone, dofetilide, dronedarone, ibutilide, sotalol); certain antipsychotics (e.g. haloperidol, pimozide, sertindole); certain antidepressants (e.g. citalopram, escitalopram); certain antibiotics (e.g. erythromycin, levofloxacin, moxifloxacin, spiramycin); certain antifungal agents (e.g. pentamidine); certain antimalarials (in particular halofantrine, lumefantrine); certain gastrointestinal medicinal products (e.g. cisapride, dolasetron, prucalopride); certain antihistamines (e.g. mequitazine, mizolastine); certain medicinal products used in cancer (e.g. toremifene, vandetanib, vincamine); and certain other medicinal products (e.g. bepridil, diphemanil, methadone).
Potent CYP3A4 inhibitors, regardless of their QT-prolonging effects, i.e. protease inhibitors, systemic azole antifungals and some macrolides (erythromycin, clarithromycin and telithromycin).

Domperidone – concomitant use not recommended

Moderate CYP3A4 inhibitors, i.e. diltiazem, verapamil and some macrolides.

Domperidone – concomitant use requiring caution

Caution is required with bradycardia- and hypokalaemia-inducing medicinal products, and with the macrolides involved in QT-interval prolongation, azithromycin and roxithromycin (clarithromycin is contraindicated as it is a potent CYP3A4 inhibitor). The above list of substances is representative and not exhaustive. Opioids may antagonise the effects of domperidone on gastric emptying.

4.6 Pregnancy and Lactation

Pregnancy

Rabeprazole: there are no data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus, although low foeto-placental transfer occurs in rats. The product is contraindicated during pregnancy.
Domperidone: there are limited post-marketing data on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown.

Breast-feeding

Rabeprazole: it is not known whether rabeprazole sodium is excreted in human breast milk and no studies in lactating women have been performed. Rabeprazole sodium is however excreted in rat mammary secretions. The product must not be used during breast-feeding.

Domperidone: domperidone is excreted in human milk and breast-fed infants receive less than 0.1% of the maternal weight-adjusted dose. The occurrence of adverse effects, in particular cardiac effects, cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue or abstain from domperidone therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Caution should be exercised where risk factors for QTc prolongation are present in breast-fed infants.

4.7 Effects on ability to drive and use machines

Neutropenia, Leucopenia, Hypersensitivity, Anorexia, Insomnia, Nervousness, Headache, Dizziness, Cough, Pharyngitis, Rhinitis, Diarrhea, Vomiting, Nausea, Abdominal pain, Constipation, Flatulence, Rash, Back pain, Asthenia, Influenza like illness, Allergic reaction, increased prolactin levels, agitation, nervousness, extrapyramidal side effects, convulsion,somnolence, headache, gastro-intestinal disorders including very rare transient intestinal cramps, very rare; diarrhea, breast pain.

4.8 Undesirable effects

Rabeprazole

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is, therefore, not dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

Domperidone

Symptoms: Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsion, disorientation, somnolence and extra pyramidal reactions.

Treatment: There is no specific antidote to Domperidone, but in the event of overdose, standard symptomatic treatment should be given immediately. Gastric lavage as well as the administration of activated charcoal, may be useful. ECG monitoring should be undertaken, because of the possibility pf QT prolongation. Close medical supervision and supportive therapy is recommended.

Anticholinergic, Anti-Parkinson drugs may be helpful in controlling extrapyramidal Reactions.

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS): https://pv.pharmacyboardkenya.org

4.9 Overdose

Rabeprazole

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

Domperidone

Symptoms: overdose has been reported primarily in infants and children. Symptoms may include agitation, altered consciousness, convulsion, disorientation, somnolence and extrapyramidal reactions.

Management: there is no specific antidote to domperidone, but in the event of overdose standard symptomatic treatment should be given immediately. Gastric lavage and the administration of activated charcoal may be useful. ECG monitoring should be undertaken because of the possibility of QT prolongation. Close medical supervision and supportive therapy are recommended. Anticholinergic and anti-Parkinson medicinal products may be helpful in controlling extrapyramidal reactions.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Rabeprazole

Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, which do not exhibit anticholinergic or H2 histamine antagonist properties but suppress gastric acid secretion by specific inhibition of the H+/K+-ATPase enzyme (the acid or proton pump). The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion, irrespective of the stimulus.

Domperidone

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

5.2 Pharmacokinetic properties

Rabeprazole – absorption

The product is an enteric-coated (gastro-resistant) pellet-in-capsule formulation, which is necessary because rabeprazole is acid-labile. Absorption therefore begins only after the capsule leaves the stomach. Absorption is rapid, with peak plasma levels occurring approximately 3.5 hours after a 20 mg dose. Cmax and AUC are linear over the dose range 10 mg to 40 mg. In healthy subjects the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and total body clearance is estimated at 283 ± 98 mL/min. There is no clinically relevant interaction with food; neither food nor the time of day of administration affects absorption.

Rabeprazole – distribution

Rabeprazole is approximately 97% bound to human plasma proteins.

Rabeprazole – metabolism and excretion

Rabeprazole sodium is metabolised through the cytochrome P450 hepatic drug metabolising system. In vitro studies with human liver microsomes indicated metabolism by CYP2C19 and CYP3A4. At expected human plasma concentrations, rabeprazole neither induces nor inhibits CYP3A4; although in vitro studies may not always be predictive of the in vivo situation, these findings indicate that no interaction is expected between rabeprazole and ciclosporin.

Domperidone – absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at approximately 1 hour after dosing. Cmax and AUC increased proportionally with dose over the 10 mg to 20 mg range. A 2- to 3-fold accumulation of AUC was observed with repeated four-times-daily dosing for 4 days. The low absolute bioavailability of oral domperidone (approximately 15%) is due to extensive first-pass metabolism in the gut wall and liver.

Domperidone – distribution

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/mL after two weeks of oral administration of 30 mg per day was almost the same as the 18 ng/mL observed after the first dose. Domperidone is 91–93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution but low brain concentration. Small amounts cross the placenta in rats.

Domperidone – metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. In vitro metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is the major cytochrome P450 form involved in N-dealkylation, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in aromatic hydroxylation.

Domperidone – excretion

Urinary and faecal excretion amount to 31% and 66% of the oral dose respectively; the proportion excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7–9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

5.3 Preclinical safety data
None.

6. Pharmaceutical Particulars

6.1 List of Excipients
Empty Gelatin Capsules Green/Green Size 2".

6.2 Incompatibilities
Not applicable.

6.3 Shelf-Life
36 months.

6.4 Special Precautions for storage
Store in a cool, dry place at a temperature below 30°C. Protect from light.

6.5 Nature and Content of container
10 capsules packed in an Alu-Alu blister pack. One such blister is packed in a printed carton together with the package insert.

6.6 Special precautions for disposal and other handling
No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder
Medcure Healthcare Ltd
P.O. Box 14609-00400, Nairobi, Kenya.
Manufacturing site
Ambix Healthcare LLP
84, Nirmal Industrial Park, GIDC, Harnahoda Road, Gozaria, Mehsana – 382825, Gujarat, India.
Email: info@ambixhealthcare.com

8. Marketing Authorization Number
H2021/CTD7782/14696

9. Date of first authorization/renewal of the authorization
2021 September 10

10. Date of revision of the text
2021 September 10