1.3.1 Summary of Product Characteristics (SPC)

1. Name of the medicinal product

Rabeprazole Sodium (EC) 20mg & Domperidone (SR) 30mg Capsules

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:

Rabeprazole Sodium.....20mg

(As enteric coated pellets)

Domperidone BP.....30mg

(As sustained release Pellets

Excipients q.s.

3. Pharmaceutical form

Solid oral dosage form, hard gelatin capsules

Chocolate coloured cap with Chocolate coloured body, hard gelatin capsules filled with orange & reddish chocolate coloured pellets.

4. Clinical particulars

4.1 Therapeutic indications

Indicated for the relief of the following:

1. Dyspepsia
2. GERD
3. Nausea associated with acid peptic disorders
4. Post-operative nausea and vomiting
5. Chronic gastritis

4.2 Posology and method of administration

One capsule once daily.

Method of administration

Capsule for oral administration.

4.3 Contraindications

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

Domperidone is contraindicated in the following situations: Known hypersensitivity to Domperidone or any of the excipients. Prolactin-releasing pituitary tumour (prolactinoma).

Domperidone should not be used when stimulation of gastric motility could be harmful: gastrointestinal haemorrhage, mechanical obstruction or perforation.

4.4 Special warnings and precautions for use

Rabeprazole

Presence of Gastric Malignancy

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Concomitant Use with Warfarin

Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased INR and prothrombin time in patients receiving a PPI and warfarin concomitantly. Increases in the INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with a PPI and warfarin concomitantly may need to be monitored for increases in the INR and prothrombin time.

Clostridium difficile-associated Diarrhoea

Published observational studies suggest that PPI therapy such as rabeprazole sodium may be associated with an increased risk of *C. difficile*-associated diarrhoea (CDAD), especially in hospitalized patients. This diagnosis should be considered for diarrhoea that does not improve.

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

CDAD has been reported with use of nearly all antibacterial agents.

Bone Fracture

Several published observational studies in adults suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g. diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Concomitant Use of Rabeprazole Sodium with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at a high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

Domperidone

Precautions for Use

The film-coated tablets contain lactose and may be unsuitable for patients with lactose intolerance, galactosaemia or glucose/galactose malabsorption. This medicinal product contains 0.97 mmol (0.04 2mg) of sodium per tablet. To be taken into consideration by patients on a controlled sodium dose.

Use During Lactation

The total amount of domperidone excreted in human breast milk is expected to be less than 7 micrograms per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore breastfeeding is not recommended for mothers who are taking domperidone.

Use in Infants

Neurological side effects are rare. Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life, the risk of neurological side effects is higher in young children. Therefore, it is recommended that the dose be determined accurately and followed strictly in children.

Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

Use in Liver Disorders

Since domperidone is highly metabolized in the liver, domperidone should be not be used in patients with hepatic impairment.

Renal Impairment

In patients with severe renal insufficiency (serum creatinine>6 mg/100 mL, i.e. >0.6 m mol/L) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours, but plasma drug levels were lower than in healthy volunteers. Since very little unchanged drug is excreted via the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency. However, on repeated administration, the dosing frequency should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly.

Cardiovascular Effects

Some epidemiological studies showed that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death.The risk may be higher in patients older than 60 years and at daily doses of more than 30 mg. Domperidone should be used at the lowest effective dose in adults and children.

Use of domperidone and other drugs that prolong QTc intervals requires that caution be exercised in patients who have existing prolongation of cardiac conduction intervals, particularly QTc patients with significant electrolyte disturbances of underlying cardiac diseases such as congestive heart failure.

Use with Potent CYP3A4 Inhibitors

Co-administration with oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors that prolong the QTc interval should be avoided. A slight increase of QT interval (mean less than 10msec) was reported in a drug-drug interaction study with oral ketoconazole. Even if the significance of this study is not fully clear, alternative therapeutic options should be considered if antifungal treatment is required.

4.5 Interaction with other medicinal products and other forms of interaction

Rabeprazole

Drugs Metabolized by CYP450

Rabeprazole is metabolized by the CYP450 drug-metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). Steady state interactions of rabeprazole and other drugs metabolized by this enzyme system have not been studied in patients.

Warfarin

There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole, and warfarin concomitantly. Increases in the INR and prothrombin time may lead to abnormal bleeding and even death

Cyclosporine

In vitro incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC50 of 62 micromolar, a concentration that is over 50 times higher than the Cmax in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Compounds Dependent on Gastric pH for Absorption

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds that are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, co-administration of rabeprazole 20 mg q.d. resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and Cmax for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of

rabeprazole and antacids produced no clinically relevant changes in plasma Rabeprazole concentrations.

Concomitant use of atazanavir and PPIs is not recommended. Co-administration of atazanavir with PPIs is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Drugs Metabolized by CYP2C19

In a clinical study in Japan evaluating rabeprazole in adult patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared with extensive metabolizers. This could be due to higher rabeprazole plasma levels in poor metabolizers. Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied.

Combined Administration with Clarithromycin

Combined administration consisting of rabeprazole, amoxicillin, and clarithromycin resulted in increases in plasma concentrations of rabeprazole and 14-hydroxyclarithromycin.

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions. Because of these drug interactions, clarithromycin is contraindicated for co-administration with certain drugs.

Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

Clopidogrel

Concomitant administration of rabeprazole and clopidogrel in healthy subjects had no clinically meaningful effect on exposure to the active metabolite of clopidogrel. No dose adjustment of clopidogrel is necessary when administered with an approved dose of rabeprazole sodium.

Domperidone

The main metabolic pathway of domperidone is through CYP3A4. *In vitro* data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone. Separate *in vivo* Pharmacokinetic / pharmacodynamic interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4-mediated first-pass metabolism by ketoconazole.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of domperidone 10mg four times daily and oral erythromycin 500 mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the Cmax and the AUC of domperidone at the steady state were increased approximately three-fold in each of these interaction studies. In these studies, domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200mg twice daily) and erythromycin monotherapy (500mg three times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

A QT-prolonging effect could not be detected when domperidone was given alone in patients with no comorbidity, even at high oral doses (up to 160mg/day).

The results of this interaction study should be taken into account when prescribing Domperidone concomitantly with strong CYP3A4 inhibitors,e.g. ketoconazole, ritonavir and erythromycin.

Opioids may antagonise the effects of domperidone on gastric emptying.

Renal Impairment

GASTOCURE DSR Capsules should be used with caution in patients with renal impairment or in those at risk of fluid retention. In patients with severe renal impairment (serum creatinine more than 6 mg/100 mL, i.e., more than 0.6mmol/L),the elimination half-life of domperidone was increased. The dosing frequency should be altered, depending on the severity of impairment, and the dose may need to be reduced. Patients on prolonged therapy should be reviewed regularly.

Hepatic Impairment

Since domperidone is highly metabolized in the liver **GASTOCURE DSR Capsules** should be not be used in patients with hepatic impairment.

Paediatric Use

The safety and effectiveness of this product in paediatric patients has not been established.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

Since many drugs are excreted in human milk, caution should be exercised when this drug is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

Rabeprazole

Worldwide, over 2,900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment.

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Studies Experience

Adults

The data described below reflect exposure to rabeprazole sodium in 1,064 adult patients exposed for up to 8 weeks. The studies were primarily placebo- and active-controlled trials in adult patients with erosive or ulcerative GERD, duodenal ulcers and gastric ulcers. The population had a mean age of 53 years (range, 18 89 years) and had a ratio of approximately 60% male: 40% female. The racial distribution was 86% Caucasian, 8% African-American, 2% Asian, and 5% other. Most patients received 10 mg, 20 mg or 40 mg/day of rabeprazole sodium.

An analysis of adverse reactions appearing in ≥2% of rabeprazole sodium patients (n=1,064) and with a greater frequency than placebo (n=89) in controlled North American and European acute treatment trials, revealed the following adverse reactions: pain (3% vs 1%), pharyngitis (3% vs 2%), flatulence (3% vs 1%), infection (2% vs 1%), and constipation (2% vs 1%).

Three long-term maintenance studies consisted of a total of 740 adult patients; at least 54% of adult patients were exposed to rabeprazole for 6 months and at least 33% were exposed for 12 months. Of the 740 adult patients, 247 (33%) and 241 (33%) patients

received 10 mg and 20 mg of Rabeprazole sodium, respectively, while 169 (23%) patients received placebo and 83 (11%) received omeprazole.

The safety profile of rabeprazole in the maintenance studies in adults was consistent with what was observed in the acute studies.

Other adverse reactions seen in controlled clinical trials, which do not meet the above criteria (≥ 2% of rabeprazole sodium treated patients and greater than placebo) and for which there is a possibility of a causal relationship to rabeprazole, include the following: headache, abdominal pain, diarrhea, dry mouth, dizziness, peripheral edema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

Combination Treatment with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with RAC, no adverse reactions unique to this drug combination were observed. In the US multicentre study, the most frequently reported drug-related adverse reactions for patients who received RAC therapy for 7 or 10 days were diarrhoea (8% and 7%) and taste perversion (6% and 10%), respectively.

No clinically significant laboratory abnormalities particular to the drug combinations were observed.

Paediatric

In a multicentre, open-label study of adolescent patients, 12 to 16 years of age, with a clinical diagnosis of symptomatic GERD or endoscopically proven GERD, the adverse event profile was similar to that of adults. The adverse reactions reported without regard to relationship to rabeprazole sodium that occurred in ≥2% of 111 patients were headache (9.9%), diarrhoea (4.5%), nausea (4.5%), vomiting (3.6%), and abdominal pain (3.6%). The related reported adverse reactions that occurred in ≥2% of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in this study that were not previously observed in adults.

Post marketing Experience

The following adverse reactions have been identified during post-approval use of Rabeprazole sodium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: sudden death; coma, hyper-ammonaemia; jaundice; rhabdomyolysis; disorientation and delirium; anaphylaxis; angio-oedema; bullous and other drug eruptions of the skin; severe dermatologic reactions, including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, and erythema multiforme; interstitial pneumonia; interstitial nephritis; TSH elevations; bone fractures; hypomagnesaemia and *C. difficile*-associated diarrhoea. In addition, agranulocytosis, haemolytic anaemia, leucopenia, pancytopenia and thrombocytopenia have been reported. Increases in prothrombin time/INR in patients treated with concomitant warfarin have been reported.

Domperidone

The adverse drug reactions are ranked below by frequency, using the following convention: very common (≥1/10), common (≥1/100, to <1/10); uncommon (≥1/1,000, to <1/100); rare (≥1/10,000, to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data).

- **Immune System Disorders**

  Very rare: Allergic reaction, including anaphylaxis, anaphylactic shock, anaphylactic reaction and angio-oedema.
- **Endocrine Disorders**

  Rare: Increased prolactin levels.
- **Psychiatric System Disorders**

  Very rare: Agitation, nervousness.
- **Nervous System Disorders**

  Very rare: Extrapyramidal side effects, convulsion, somnolence, headache.

  Not known: Dystonia.
- **Eye Disorders**

  Not known: Oculogyric crisis.

- **Cardiac Disorders**

  Not known: Prolongation of QT interval;

  Not known: Ventricular arrhythmias or sudden cardiac death also occur. Torsades de pointes has been reported with intravenous domperidone; however, the possibility of this risk should be considered with oral forms of domperidone.
- **GastroIntestinal Disorders**

  Rare: Gastrointestinal disorders, including very rare transient intestinal cramps.

  Very rare: Diarrhoea.
- **Skin and Subcutaneous Tissue Disorders**

  Very rare: Urticaria, pruritus, rashes.
- **Reproductive System and Breast Disorders**

  Uncommon: Breast pain.

  Rare: Galactorrhoea, gynaecomastia, amenorrhoea.

  Not known:Reduced libido.
- **Investigations**

  Very rare: Liver function test abnormal.

As the hypophysis is outside the blood-brain barrier, domperidone may cause an increase in prolactin levels. In rare cases, this hyperprolactinaemia may lead to neuro-endrocrinological side effects such as galactorrhoea, gynaecomastia and amenorrhoea. Extrapyramidal side effects are exceptional in adults. These side effects reverse spontaneously and completely as soon as treatment is stopped.

Other central nervous system-related effects of convulsion, agitation and somnolence also are very rare and primarily reported in infants and children.

4.9 Overdose

Rabeprazole

There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdosage with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to

120 mg rabeprazole q.d. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein-bound and is not readily dialysable. In the event of overdosage, treatment should be symptomatic and supportive.

Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoactivity, laboured respiration, lateral or prone position and convulsion in mice and rats and watery diarrhoea, tremor, convulsion and coma in dogs.

Domperidone

Symptoms

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

Treatment

There is no specific antidote to domperidone, but in the event of overdose, gastric lavage as well as the administration of activated charcoal, may be useful. Close medical supervision and supportive therapy is recommended. Anticholinergic, anti-Parkinson drugs may be helpful in controlling extrapyramidal reactions.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Rabeprazole

Mechanism of Action

Rabeprazole sodium belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H+, K+ ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has

been characterized as a gastric PPI. Rabeprazole blocks the final step of gastric acid secretion.

In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulphenamide. When studied *in vitro*, rabeprazole is chemically activated at pH 1.2, with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles, with a half-life of 90 seconds.

Antisecretory Activity

The antisecretory effect begins within one hour after oral administration of 20 mg Rabeprazole sodium. The median inhibitory effect of rabeprazole sodium on 24 hour gastric acidity is 88% of maximal after the first dose. Rabeprazole sodium 20 mg inhibits basal and peptone meal-stimulated acid secretion versus placebo by 86% and 95%, respectively, and increases the percent of a 24-hour period that the gastric pH>3 from 10% to 65% (see table below). This relatively prolonged pharmacodynamic action compared with the short pharmacokinetic half-life (1-2 hours) reflects the sustained inactivation of the H+, K+ATPase.

Gastric acid parameters rabeprazole sodium versus placebo after 7 days of once-daily dosing

Parameter	Rabeprazole Sodium (20 mg q.d.)	Placebo
Basal Acid Output (mmol/hr)	0.4*	2.8
Stimulated Acid Output (mmol/hr)	0.6*	13.3
% Time Gastric pH>3	65*	10

*(p <0.01 versus placebo)

Compared with placebo, rabeprazole sodium, 10 mg, 20 mg, and 40 mg, administered once daily for 7 days significantly decreased intragastric acidity with all doses for each of four meal-related intervals and the 24-hour time period overall. In this study, there were no statistically significant differences between doses; however, there was a significant dose-related decrease in intragastric acidity. The ability of rabeprazole to cause a dose-related decrease in mean intragastric acidity is illustrated below.

AUC acidity (mmolhr/l) rabeprazole sodium versus placebo on day 7 of once-daily dosing (Mean±SD)

AUC Interval	Treatment			
	Rabeprazole 10 mg	Rabeprazole 20 mg	Rabeprazole 40 mg	Placebo
(hrs)	(N=24)	(N=24)	(N=24)	(N=24)
08:00-13:00	19.6±21.5*	12.9±23*	7.6±14.7*	91.1±39.7
13:00-19:00	5.6±9.7*	8.3±29.8*	1.3±5.2*	95.5±48.7
19:00-22:00	0.1±0.1*	0.1±0.06*	0.0±0.02*	11.9±12.5
22:00-08:00	129.2±84*	109.6±67.2*	76.9±58.4*	479.9±165
$AUC_{0\text{-}24\ hours}$	155.5±90.6*	130.9±81*	85.8±64.3*	678.5±216

*(p <0.01 versus placebo)

After administration of 20 mg rabeprazole sodium tablets once daily for 8 days, the mean percent of time that gastric pH>3 or gastric pH>4 after a single dose (Day 1) and multiple doses (Day 8) was significantly greater than placebo (see table below). The decrease in gastric acidity and the increase in gastric pH observed with 20 mg rabeprazole sodium tablets administered once daily for 8 days were compared with the same parameters for placebo, as illustrated below:

Gastric acid parameters for rabeprazole sodium once-daily dosing versus placebo on day 1 and day 8

Parameter	Rabeprazole Sodium 20 mg q.d.		Placebo	
	Day 1	Day 8	Day 1	Day 8
Mean $AUC_{0\text{-}24}$ Acidity	340.8*	176.9*	925.5	862.4
Median trough pH (23 hours)[a]	3.77	3.51	1.27	1.38
% Time Gastric pH>3[b]	54.6*	68.7*	19.1	21.7
% Time Gastric pH>4[b]	44.1*	60.3*	7.6	11.0

[a]No inferential statistics conducted for this parameter.

*(p <0.01 versus placebo)

[b]Gastric pH was measured every hour over a 24-hour period.

Effects on Oesophageal Acid Exposure

In patients with gastro-oesophageal reflux disease (GERD) and moderate-to-severe oesophageal acid exposure, rabeprazole sodium 20 mg and 40 mg tablets per day decreased 24-hour oesophageal acid exposure. After 7 days of treatment, the percentage of time that oesophageal pH4 for at least 35% of the 24-hour period; this level was achieved in 90% of subjects receiving rabeprazole sodium 20 mg and in 100% of subjects

receiving rabeprazole sodium 40 mg. With rabeprazole sodium 20 mg and 40 mg per day, significant effects on gastric and oesophageal pH were noted after 1 day of treatment, and more pronounced after 7 days of treatment.

Effects on Serum Gastrin

In patients given daily doses of rabeprazole sodium for up to 8 weeks to treat ulcerative or erosive oesophagitis and in patients treated for up to 52 weeks to prevent recurrence of disease, the median fasting gastrin level increased in a dose-related manner. The group median values stayed within the normal range.

In a group of subjects treated daily with rabeprazole sodium 20 mg tablets for 4 weeks a doubling of mean serum gastrin concentrations were observed. Approximately 35% of these treated subjects developed serum gastrin concentrations above the upper limit of normal. In a study of cytochrome (CY) P2C19genotyped subjects in Japan, poor metabolizers developed statistically significantly higher serum gastrin concentrations than extensive metabolizers.

Effects on Enterochromaffin-like (ECL) Cells

Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially in females.

In over 400 patients treated with rabeprazole sodium tablets (10 or 20 mg/day) for up to 1 year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the PPI. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Endocrine Effects

Studies in humans for up to 1 year have not revealed clinically significant effects on the endocrine system. In healthy male volunteers treated with rabeprazole sodium for 13 days, no clinically relevant changes have been detected in the following endocrine

parameters examined: 17 betaoestradiol, thyroid-stimulating hormone, tri-iodothyronine, thyroxine, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteotrophic hormone, prolactin, somatotrophic hormone, dehydroepiandrosterone, cortisol-binding globulin, and urinary 6beta-hydroxycortisol, serum testosterone, and circadian cortisol profile.

Other Effects

In humans treated with rabeprazole sodium for up to 1 year, no systemic effects have been observed on the central nervous, lymphoid, haematopoietic, renal, hepatic, cardiovascular or respiratory systems. No data are available on long-term treatment with rabeprazole sodium and ocular effects.

Microbiology

The following *in vitro* data are available but the clinical significance is unknown.

Rabeprazole sodium, amoxicillin and clarithromycin as a three-drug regimen has been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections.

H. pylori

Susceptibility testing of H. pylori isolates was performed for amoxicillin and clarithromycin using the agar dilution methodology, and minimum inhibitory concentrations (MICs) were determined.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

Incidence of Antibiotic-Resistant Organisms among Clinical Isolates

Pre-treatment Resistance

Clarithromycin pre-treatment resistance rate (MIC ≥1 μg/mL) to *H. pylori* was 9% (51/560) at baseline in all treatment groups combined. A total of >99% (558/560) of patients had *H. Pylori* isolates that were considered to be susceptible (MIC ≤0.25 μg/mL)

to amoxicillin at baseline. In 2 patients, baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 µg/mL were seen.

Clarithromycin susceptibility test results and clinical/bacteriologic outcomes[a] for a three-drug regimen (Rabeprazole 20 mg twice daily, Amoxicillin 1,000 mg twice daily, and Clarithromycin 500 mg twice daily for 7 or 10 Days)

Days of RAC Therapy	Clarithromycin Pre-treatment Results	Total Number	*H.pylori*-Negative(Eradicated)	*H.pylori*-Positive (Persistent) Post-Treatment Susceptibility Results			
				S[b]			
7	Susceptible[b]	129	103	2	7	Susceptible[b]	129
7	Intermediate[b]	0	0	0	7	Intermediate[b]	0
7	Resistant[b]	16	5	2	7	Resistant[b]	16
10	Susceptible[b]	133	111	3	10	Susceptible[b]	133
10	Intermediate[b]	0	0	0	10	Intermediate[b]	0
10	Resistant[b]	9	1	0	10	Resistant[b]	9

[a] Includes only patients with pre-treatment and post-treatment clarithromycin susceptibility test results.

[b] Susceptible (S) MIC ≤0.25 µg/mL, Intermediate (I) MIC = 0.5 µg/mL, Resistant (R) MIC ≥1 µg/mL
RAC = rabeprazole plus amoxicillin and clarithromycin

Patients with persistent *H.pylori* infection following rabeprazole, amoxicillin, and clarithromycin therapy will likely have clarithromycin resistant clinical isolates. Therefore, clarithromycin susceptibility testing should be done when possible. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the US multicentre study, a total of >99% (558/560) of patients had *H. pylori* isolates that were considered to be susceptible (MIC ≤0.25 µg/mL) to amoxicillin at baseline. The other 2 patients had baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 µg/mL, and both isolates were clarithromycin-resistant at baseline; in one case, *H. pylori* was eradicated. In the 7- and 10-day treatment groups,*H. pylori* was eradicated in 75% (107/145) and 79% (112/142), respectively, of the patients who had pre-treatment amoxicillin-susceptible MICs (≤0.25 µg/mL). No patients developed amoxicillin-resistant *H. pylori* during therapy.

Domperidone

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in 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.

Studies in humans have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

5.2 Pharmacokinetic properties

Rabeprazole

Rabeprazole sodium delayed-release tablets are enteric-coated to allow rabeprazole sodium, which is acid-labile, to pass through the stomach relatively intact.

After oral administration of 20 mg rabeprazole, peak plasma concentrations (Cmax) of Rabeprazole occur over a range of 2.0 to 5.0 hours (Tmax). The rabeprazole Cmax and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10-40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole is not altered by multiple dosing.

Absorption

Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared with intravenous administration) is approximately 52%. When rabeprazole sodium tablets are administered with a high fat meal, Tmax is variable; which concomitant food intake may delay the absorption up to 4 hours or longer. However, the Cmax and the extent of rabeprazole absorption (AUC) are not significantly altered. Thus, rabeprazole sodium tablets may be taken without regard to timing of meals.

Distribution

Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism

Rabeprazole is extensively metabolized. A significant portion of rabeprazole is metabolized via systemic nonenzymatic reduction to a thioether compound. Rabeprazole is also metabolized to sulphone and desmethyl compounds via CYP450 in the liver. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. *In vitro*studies have demonstrated that rabeprazole is metabolized in the liver primarily by CYP450 3A (CYP3A) to a sulphone metabolite and CYP450 2C19 (CYP2C19) (CYP2C19) to desmethylrabeprazole. CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3-5% of Caucasians and 17-20% of Asians). Rabeprazole metabolism is slow in these sub-populations; therefore, they are referred to as poor metabolizers of the drug.

Elimination

Following a single 20 mg oral dose of 14 C-labelled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the faeces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or faeces.

Special Populations

Geriatric

In 20 healthy elderly subjects, after oral administration of rabeprazole 20 mg tablets once daily for 7 days, AUC values approximately doubled and the Cmax increased by 60% compared with values in a parallel younger control group. There was no evidence of drug accumulation after once-daily administration.

Paediatric

The pharmacokinetics of rabeprazole was studied in paediatric patients with GERD, aged 12 to 16 years.

Patients, 12 to 16 Years of Age

The pharmacokinetics of rabeprazole was studied in 12 adolescent patients (12 to 16 years of age) with GERD, in a multicentre study. Patients received rabeprazole 20 mg tablets once daily for 5 or 7 days. An approximate 40% increase in exposure was noted following 5-7 days of dosing compared with the exposure after 1-day dosing.

Pharmacokinetic parameters in adolescent patients with GERD, 12 to 16 years of age, were within the range observed in healthy adult volunteers.

Gender and Race

In analyses adjusted for body mass and height, rabeprazole pharmacokinetics showed no clinically significant differences between male and female subjects. In studies that used different formulations of rabeprazole, AUC0-infinity values for healthy Japanese men were approximately 50-60% greater than values derived from pooled data from healthy men in the United States.

Renal Impairment

In 10 patients with stable end-stage renal disease requiring maintenance haemodialysis (creatinine clearance ≤5 mL/min/1.73 m2), no clinically significant differences were observed in the pharmacokinetics of rabeprazole after a single 20 mg oral dose when compared with 10 healthy volunteers .

Hepatic Impairment

In a single-dose study of 10 patients with chronic mild-to-moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC0-24 was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared with values in healthy men.

In a multiple-dose study of 12 patients with mild-to-moderate hepatic impairment administered 20 mg rabeprazole once daily for 8 days, AUC0-infinity and Cmax values increased approximately 20% compared with values in healthy age- and gender-matched subjects. These increases were not statistically significant. No information exists on rabeprazole disposition in patients with severe hepatic impairment.

In 16 healthy volunteers genotyped as extensive metabolizers with respect to CYP2C19, 20 mg rabeprazole sodium, 1,000 mg amoxicillin, 500 mg clarithromycin, or all three drugs were administered in a four-way crossover study. Each of the four regimens was administered twice daily for 6 days. The AUC and Cmax for clarithromycin and amoxicillin were not different following combined administration compared with values following single administration. However, the rabeprazole AUC and Cmax increased by 11% and 34%, respectively, following combined administration. The AUC and Cmax for 14-hydroxyclarithromycin (active metabolite of clarithromycin) also increased by 42%

and 46%, respectively. This increase in exposure to rabeprazole and 14-hydroxyclarithromycin is not expected to produce safety concerns.

Concomitant Use with Clopidogrel

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects including CYP2C19 extensive and intermediate metabolizers receiving once daily administration of clopidogrel 75 mg concomitantly with placebo or with rabeprazole sodium 20 mg (n=36), for 7 days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 12% (mean AUC ratio was 88%, with 90% CI of 81.7-95.5%) when rabeprazole sodium was coadministered, compared with administration of clopidogrel with placebo.

Domperidone

Absorption

In fasting subjects, domperidone is rapidly absorbed after oral administration with peak plasma concentrations at 30-60 minutes. The low absolute bioavailability of oral Domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastrointestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

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 2 weeks of oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins.

Distribution studies with radio labelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N dealkylation *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of CYP450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 AND CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and faecal excretions amount to 31% and 66% of the oral dose, respectively. The proportion of the drug 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

No data available.

6. Pharmaceutical particulars

6.1 List of excipients

Chocolate / chocolate Empty hard gelatin capsules size “2”

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C, Protected from light & moisture.

Keep medicine out of reach of children.

6.5 Nature and contents of container

1 x10 Capsules packs in a unit carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

PHARMA ETHICS LTD.

39, Oritse Street, Ikeja, Lagos,

Nigeria