FIRST FOLD SHOULD BE HORIZONTAL & REMAINING VERTICAL

RAPEED 20

Rabeprazole sodium gastro-resistant Tablets 20mg

COMPOSITION
Each gastro-resistant tablet contains:
Rabeprazole sodium ……. 20 mg

PRODUCT DESCRIPTION
Yellow, round, biconvex, beveled, enteric-coated tablets, imprinted '20' in black on one side.

PHARMACODYNAMICS PROPERTIES
Pharmacotherapeutic group: Alimentary tract and metabolism, Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), PPIs, ATC code: A02B C04

Mechanism of action
Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by the 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. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

Anti-secretory activity
After oral administration of a 20 mg dose of rabeprazole sodium the onset of the anti-secretory effect occurs within one hour, with the maximum effect occurring within two to four hours. Inhibition of basal and food stimulated acid secretion 23 hours after the first dose of rabeprazole sodium are 69% and 82% respectively and the duration of inhibition lasts up to 48 hours. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.
Decreased gastric acidity due to any means, including PPIs such as rabeprazole, increases counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs may possibly increase the risk of gastrointestinal infections such as Salmonella, Campylobacter and Clostridium difficile.

Serum gastrin effects
Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion and remained stable while treatment was continued. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy.
Human gastric biopsy specimens from the antrum and the fundus have not detected changes in ECL cell histology, degree of gastritis, incidence of atrophic gastritis, intestinal metaplasia or distribution of H. pylori infection. No significant change in findings present at baseline was observed.

Other effects
Systemic effects of rabeprazole sodium in the CNS, cardiovascular and respiratory systems have not been found to date. Rabeprazole sodium, given in oral doses of 20 mg for 2 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, oestrogen, testosterone, prolactin, cholecystokinin, secretin, glucagon, follicle stimulating hormone (FSH), luteinising hormone (LH), renin, aldosterone or somatotrophic hormone.
It is shown that rabeprazole sodium does not have clinically significant interactions with amoxicillin. Rabeprazole does not adversely influence plasma concentrations of amoxicillin or clarithromycin when co-administered for the purpose of eradicating upper gastrointestinal H. pylori infection.
During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.
Available published evidence suggests that PPIs should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

PHARMACOKINETIC PROPERTIES
Absorption
Rapeed is an enteric-coated (gastro-resistant) tablet formulation of rabeprazole sodium. This presentation is necessary because rabeprazole is acid-labile.
Absorption of rabeprazole therefore begins only after the tablet leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (Cmax) of rabeprazole and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism. Additionally the bioavailability does not appear to increase with repeat administration. The plasma half-life is approximately one hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. There was no clinically relevant interaction with food. Neither food nor the time of day of administration of the treatment affect the absorption of rabeprazole sodium.

Distribution
Rabeprazole is approximately 97% bound to human plasma proteins.

Metabolism and excretion
Rabeprazole sodium, as is the case with other members of the PPI class of compounds, is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolising system. Rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4). At expected human plasma concentrations rabeprazole neither induces nor inhibits CYP3A4; and no interaction is expected between rabeprazole and cyclosporin. In humans the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but it is not present in plasma.
Following a single 20 mg 14C labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in faeces.

Gender
Adjusted for body mass and height, there are no significant gender differences in pharmacokinetic parameters following a single 20 mg dose of rabeprazole.

Renal dysfunction
In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤5ml/min/1.73 m^2), the disposition of rabeprazole was very similar to that in healthy patients. The AUC and the Cmax in these patients was about 35% lower than the corresponding parameters in healthy patients. The mean half-life of rabeprazole was 0.82 hours in healthy patients, 0.95 hours in patients during haemodialysis and 3.6 hours post dialysis. The clearance of the drug in patients with renal disease requiring maintenance haemodialysis was approximately twice that in healthy patients

Hepatic dysfunction
Following a single 20 mg dose of rabeprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there was a 2-3 fold increase in half-life of rabeprazole. However, following a 20 mg dose daily for 7 days the AUC had increased to only 1.5-fold and the Cmax to only 1.2-fold. The half-life of rabeprazole in patients with hepatic impairment was 12.3 hours compared to 2.1 hours in healthy patients. The pharmacodynamic response (gastric pH control) in both was clinically comparable.

Older people
Elimination of rabeprazole was somewhat decreased in older people. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled, the Cmax increased by 60% and t½ increased by approximately 30% as compared to young healthy patients. However there was no evidence of rabeprazole accumulation.

CYP2C19 polymorphism
Following a 20 mg daily dose of rabeprazole for 7 days, CYP2C19 slow metabolisers, had AUC and t½ which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolisers whilst Cmax had increased by only 40%.

INDICATION
Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)
Rapeed is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of Rapeed may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)
Rapeed is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD maintenance).

Healing of Duodenal Ulcers
Rapeed is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome
Rapeed is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger- Ellison Syndrome.

Symptomatic treatment of moderate to very severe Gastroesophageal reflux disease (symptomatic GERD)
Rapeed is indicated for the symptomatic treatment of moderate to very severe GERD.

Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence in Adults
Rapeed in combination with amoxicillin and clarithromycin as a three drug regimen, is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or history within the past 5 years) to eradicate H. Pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence. In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

DOSAGE AND ADMINISTRATION
The usual adult dose for oral use is 10 mg of sodium rabeprazole administered once daily. However, the dosage may be increased up to 20 mg orally once daily depending on the severity of symptoms.

Adults/elderly:
Healing of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GERD):
The recommended oral dose for this condition is 20 mg to be taken once daily for four to eight weeks. Doses of 10 mg or 20 mg twice daily may be administered orally to reflux esophagitis patients for a further 8 weeks when proton pump inhibitor treatment is ineffective. However, a dose of 20 mg twice daily should only be administered to patients with severe mucosa injury.

Gastro-Oesophageal Reflux Disease Long-term Management (GERD Maintenance):
For long-term management, a maintenance dose of PARJET 20 mg or 10 mg once daily can be used depending upon patient response.
For the maintenance therapy of reflux esophagitis when proton pump inhibitor treatment is ineffective, dose of 10 mg twice daily may be administered orally.

Zollinger-Ellison Syndrome:
The recommended adult starting dose is 60 mg once a day. The dose may be titrated upwards to 120 mg/day based on individual patient needs. Single daily doses up to 100 mg/day may be given. 120 mg dose may require divided doses, 60 mg twice daily. Treatment should continue for as long as clinically indicated.

Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GERD):
10 mg once daily in patients without oesophagitis. If symptom control has not been achieved during four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen taking 10 mg once daily when needed.

Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence In Adults
Three Drug Regimen[a]

Rapeed	20mg	Twice Daily for 7 days
Amoxicillin	1000mg	Twice Daily for 7 days
Clarithromycin	500mg	Twice Daily for 7 days

All three medications should be taken twice daily with the morning and evening meals.

[a]It is important that patients comply with the full 7-day regimen
For indications requiring once daily treatment Rapeed tablets should be taken in the morning, before eating; and although neither the time of day nor food intake was shown to have any effect on rabeprazole sodium activity, this regimen will facilitate treatment compliance.
Patients should be cautioned that the Rapeed tablets should not be chewed or crushed, but should be swallowed whole.

Renal and hepatic impairment
No dosage adjustment is necessary for patients with renal or hepatic impairment.

Children
Rapeed is not recommended for use in children, as there is no experience of its use in this group.

Precaution
The patient should be carefully observed during administration and the cumulative dose should be kept to a minimum for the particular symptoms being treated.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients
Rapeed is contra-indicated in pregnancy and during breast feeding

WARNING AND PRECAUTIONS
Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with Rapeed.

A risk of cross-hypersensitivity reactions with other proton pump inhibitor or substituted benzimidazoles cannot be excluded.

Patients should be cautioned that Rapeed tablets should not be chewed or crushed, but should be swallowed whole.

Rapeed is not recommended for use in children, as there is no experience of its use in this group.

In the majority of cases of blood dyscrasias (thrombocytopenia and neutropenia) where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

In the majority of hepatic enzyme abnormalities cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

There are no clinical data on the use of Rapeed in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rapeed is first initiated in such patients.

Co-administration of atazanavir with Rapeed is not recommended.

Treatment with proton pump inhibitors, including Rapeed, may possibly increase the risk of gastrointestinal infections such as Salmonella, Campylobacter and Clostridium difficile.

Regular Surveillance*
Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance.

Subacute cutaneous lupus erythematosus (SCLE)*
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun- exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Rapeed. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Hypomagnesaemia*
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors like Rapeed for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the proton pump inhibitor.

For patients expected to be on prolonged treatment or who take proton pump inhibitors with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting proton pump inhibitor treatment and periodically during treatment.

Concomitant use of Rabeprazole with Methotrexate
Concomitant use of PPIs with methotrexate (primarily at 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.

Fracture*
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Clostridium Difficile diarrhea*
Published observational studies suggest that proton pump inhibitor therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Vitamin B12 Deficiency*
Daily treatment with any acid-suppressing medication over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Interference with laboratory tests**
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. If the patient(s) are due to have a test on Chromogranin A level, Rapeed treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

*NPRA Directive Bil 16 2017
**DRGD Second Edition – September 2016, revised January 2019

INTERACTION WITH OTHER MEDICAMENTS
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. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with Rapeed.
Antacids were used concomitantly with the administration of Rapeed and no interaction with liquid antacids was observed.
Co-administration of atazanavir 300 mg/ritonavir 100 mg 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 PPIs. Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir.

Methotrexate
Case reports 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.

PREGNANCY AND LACTATION
Pregnancy
There are no data on the safety of rabeprazole in human pregnancy.
Data from rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Rapeed is contraindicated during pregnancy.

Breast feeding
It is not known whether rabeprazole sodium is excreted in human breast milk. No studies in breast-feeding women have been performed. Rabeprazole sodium is however excreted in rat mammary secretions. Therefore Rapeed should not be used during breast feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that Rapeed would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

SIDE EFFECTS
The most commonly reported adverse drug reactions were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse event were mild or moderate in severity, and transient in nature. Frequencies are defined as: common, uncommon, rare, very rare, not known.

System Organ Class	Adverse Events	Frequency
Infections and infestations	*Clostridium difficile* associated diarrhea[4]	-
Blood and lymphatic systemdisorders	Neutropenia,leucopenia, thrombocytopenia, leukocytosis	Rare
Immune system disorders	Hypersensitivity[1,2]	Rare
Metabolism and nutrition disorders	Anorexia	Rare
	Hypomagnesaemia[4], hyponatremia	Not Known
	Vitamin B12 deficiency4	-
	Insomnia	Common
Psychiatric disorders	Nervousness	Uncommon
	Depression	Rare
	Confusion	Not Known
Nervous system disorders	Headache, dizziness	Common
	Somnolence	Uncommon
Eye disorders	Visual disturbance	Rare
Vascular disorders	Peripheral Oedema	Not Known
Respiratory, thoracic and mediastinal disorders	Cough, pharyngitis, rhinitis	Common
	Bronchitis, sinusitis	Uncommon
Gastrointestinal disorders	Fundic gland polyps (benign) [4], diarrhoea, vomiting, nausea, abdominal pain, constipation, flatulence	Common
	Dyspepsia, dry mouth, eructation	Uncommon
	Gastritis, stomatitis, taste disturbance	Rare
	Microscopic colitis	Not known
Hepatobiliary disorders	Hepatitis, jaundice, hepatic encephalopathy[3]	Rare
Skin and subcutaneous tissue disorders	Rash, erythema2	Uncommon
	Pruritus, sweating, bullous reactions[2]	Rare
	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS)	Very Rare
	Subacute cutaneous lupus erythematosus[4]	Not Known
Musculoskeletal and connective tissue disorders	Non-specific pain, back pain	Common
	Fracture of the hip, wrist or spine[4], myalgia, leg cramps, arthralgia	Uncommon
	Hypomagnesaemia[4]	Not known
Renal and urinary disorders	Urinary tract infection	Uncommon
	Interstitial nephritis[4]	-
Reproductive system and breast disorders	Gynaecomastia	Not known
General disorders and administration site conditions	Asthenia, influenza-like illness	Common
	Chest pain, chills, pyrexia	Uncommon
Investigations	Increased hepatic enzymes[3]	Uncommon
	Weight increased	Rare

[1]: Includes facial swelling, hypotension and dyspnoea
[2]: Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.
[3]: Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rapeed is first initiated in such patients
[4]: See warnings and precautions

OVERDOSE
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 utilised.

STORAGE CONDITION
Store below 30°C. Protect from light and moisture.

DOSAGE FORM AND PACKAGING AVAILABLE
Gastro-resistant Tablets
ALU/PVC/PvDC Blister containing 10's tablet. The 3 blisters are packed into a trilaminated PET/Alu/PE bag with a silica gel packet.
Such 1 bag is packed into an outer carton with a pack insert.
3x10's Alu-Alu desiccant blister packed in a carton along with pack insert.

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