1.6.1 Summary of Products Characteristics

1. Name of the Medicinal Product:

Product Name: Barole 20 [Enteric Coated Rabeprazole Sodium Capsules 20 mg]

2. Qualitative and quantitative composition

Qualitative Declaration:

Name of Ingredients	Specification
Drug Substance	
Rabeprazole Sodium	IH
Excipients	
Non Pareil Seeds 16 – 18 # MgCO3-HPMC coated	IH
Hypromellose (E15)	BP/Ph.Eur
Sodium Hydroxide	BP/Ph.Eur
Light Magnesium Carbonate	BP/Ph.Eur
Purified Talc	BP/Ph.Eur
Methacrylic Acid Copolymer dispersion (Drug L 30 D)	NF
Macrogol (PEG -6000)	BP/Ph.Eur
Titanium Dioxide	BP/Ph.Eur
Ferric Oxide (Red)	USP-NF
Ferric Oxide (Black)	IH
Methanol	USP
Purified Water	USP/Ph.Eur
Total	

Quantitative Declaration:

Name of Ingredients	Specification	Qty./Capsule (mg)
Drug Substance		
Rabeprazole Sodium	IH	20.00
Excipients		
Non Pareil Seeds 16 – 18 # MgCO3-HPMC coated	IH	66.00
Hypromellose (E15)	BP/Ph.Eur	13.84
Sodium Hydroxide	BP/Ph.Eur	1.37

Light Magnesium Carbonate	BP/Ph.Eur	6.90
Purified Talc	BP/Ph.Eur	8.67
Methacrylic Acid Copolymer dispersion (Drug L 30 D)	NF	27.68
Macrogol (PEG -6000)	BP/Ph.Eur	2.77
Titanium Dioxide	BP/Ph.Eur	1.38
Ferric Oxide (Red)	USP-NF	1.11
Ferric Oxide (Black)	IH	0.28
Methanol	USP	60.00
Purified Water	USP/Ph.Eur	332.28
Total		**150.00**

3. Pharmaceutical Form

Brown spherical to oval pellets encapsulated in size '3' hard gelatin unprinted capsules with brown opaque cap and red opaque body and strip packed.

4. Clinical Particulars

4.1 Therapeutic Indications

Healing of Erosive or Ulcerative GERD in Adults

Rabeprazole capsules are 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 alter 8 weeks of treatment, an additional 8-week course of Rabeprazole may be considered.

Maintenance of Healing of Erosive or Ulcerative GERD in Adults

Rabeprazole capsules are indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance). Controlled studies do not extend beyond 12 months.

Treatment of SymptomatiC GERD in Adults

Rabeprazole capsules are indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD in adults for up to 4 weeks.

Healing of Duodenal Ulcers in Adults

Rabeprazole capsules are indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Helicobacter Pylori Eradication to reduce the risk of Duodenal Ulcer Recurrence in adults

Rabeprazole capsules, in combination with amoxicillin and clarithromycin as a three drug regimen, are 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.

Treatment of Pathological Hypersecretory Conditions,Including Zollinger-Ellison Syndrome in adults

Rabeprazole capsules are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

Treatment of SymptomatiC GERD in Adolescent Patients 12 Years of Age and Older

Rabeprazole capsules are indicated for the treatment of symptomatic GERD in adolescents 12 years of age and above for up to 8 weeks.

4.2 Posology and method of administration

DOSAGE AND ADMINISTRATION

Table 1 shows the recommended dosage of Rabeprazole capsules in adults and adolescent patients 12 years of age and older.

Table 1: Recommended Dosage and Duration of Rabeprazole capsules in Adults and Adolescents 12Years of Age and Older

Indication	Dosage of Rabeprazole capsules	Treatment Duration
Adults		
Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)	20 mg once daily	4 to 8 weeks*
Maintenance of Healing of Erosive or Ulcerative GERD	20 mg once daily	Controlled studies do not extend beyond 12 months
Symptomatic GERD in Adults	20 mg once daily	Up to 4 weeks**
Healing of Duodenal Ulcers	20 mg once daily after the morning meal	Up to 4 weeks***
Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence	Rabeprazole capsules 20mg Amoxicillin 1000mg Clarithromycin 500 mg Take all three medications twice daily with morning and evening meals; it is important that patients comply with the full 7-day regimen	7 - days
Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome	Starting dose 60 mg once daily then adjust to patient needs; some patients require divided doses Dosages of 100 mg once daily and 60 mg twice daily have been administered	As long as clinically indicated Some patients with Zollinger-Ellison syndrome have been treated continuously for up to one year
Adolescents 12 Years of Age and Older		
Symptomatic GERD	20 mg once daily	Up to 8 weeks

* For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of Rabeprazole capsules may be considered.
** If symptoms do not resolve completely after 4 weeks, an additional course of treatment may be considered.
*** Most patients heal within 4 weeks; some patients may require additional therapy to achieve healing.

Administration Instructions

• Swallow Rabeprazole capsules whole. Do not chew or crush capsules.

• For the treatment of duodenal ulcers take Rabeprazole capsules alter a meal.

• For *Helicobacter pylori* eradication take Rabeprazole capsules with food.

• For all other indications Rabeprazole capsules can be taken with or without food.

• Take a missed dose as soon as possible. If it is almost time for the next dose, skip the missed dose and go back to the normal schedule. Do noltaketwo doses althe same time.

4.3 Contraindications

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

4.4 Special Warnings and Precautions for Use

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 rabeprazole. Patients on long-term treatment (particularly those treated for morethan a year) should be kept under regular surveillance.

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

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

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

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

HepatiC enzyme abnormalities have been seen in clinical trials and have also been reported since market authorisation. In the majority of cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

No evidence of significant drug related safety problems was seen in a study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls.

However because there are no clinical data on the use of Rabeprazole capsules in the treatment of patients with severe hepatiC dysfunction the prescriber is advised to exercise caution when treatment with Rabeprazole capsules is first initiated in such patients.

Co-administration of atazanavir with Rabeprazole capsules is not recommended

Treatment with PPIs, including Rabeprazole capsules, may possibly increase the risk of gastrointestinal infections such as *Salmonella, Campylobacfer* and *Clostridium difficile.*

PPIs, 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 older people or in presence of other recognised risk factors. Observational studies suggest that PPIs 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.

Severe hypomagnesaemia has been reported in patients treated with PPIs like Rabeprazole tablets 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 PPI.

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

Concomitant use of rabeprazole with methotrexate

Literature suggests that 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.

Influence on vitamin B12 absorption

Rabeprazole sodium, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or a- chlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Subacute cutaneous lupus erythematosus (SCLE)

PPIs 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 Rabeprazole tablets. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPIs.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Rabeprazole tablets treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of PPI treatment.

4.5 Drug Interactions

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 Rabeprazole tablets.

In clinical trials, antacids were used concomitantly with the administration of Rabeprazole tablets and, in a specific drug-drug interaction study, 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, 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.

4.6 Pregnancy and Lactation

Pregnancy

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 due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Rabeprazole 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 rabeprazole should not be used during breast feeding.

4.7 Effects on Ability to Drive and Use Machines

Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that rabeprazole capsules would cause an impairment of driving periormance 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.

4.8 Undesirable Effects

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketing experience.

Frequencies are defined as: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (>1/10,000, <1/1000) very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations	Infection				
Blood and the lymphatic system disorders			Neutropenia Leucopenia Thrombocytopenia Leucocytosis		
Immune system disorders			Hypersensitivity[1,2]		

Metabolism and nutrition disorders			Anorexia		Hyponatremia Hypomagnesaemia[4]
Psychiatric disorders	Insomnia	Nervousness	Depression		Confusion
Nervous system disorders	Headache Dizziness	Somnolence			
Eye disorders			Visual disturbance		
Vascular disorders					Peripheral Oedema
Respiratory, thoracic and mediastinal disorders	Cough Pharyngitis Rhinitis	Bronchitis Sinusitis			
Gastrointestinal disorders	Diarrhoea Vomiting Nausea Abdominal pain Constipation Flatulence Fundic Gland Polyps (Benign)	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbance		Microscopic colitis
Hepato-biliary disorders			Hepatitis Jaundice Hepatic encephalopathy[3]		
Skin and subcutaneous tissue disorders		Rash Erythema[2]	Pruritus Sweating Bullous reactions[2]	Erythema multiforme, toxic epidermal necrolysis (TEN),	Subacute cutaneous lupus erythematosus[4]

				Stevens-Johnson syndrome (SJS)	
Musculoskeletal connective tissue and bone disorders	Non-specific pain Back pain	Myalgia Leg cramps Arthralgia Fracture of the hip, wrist or spine[4]			
Renal and urinary disorders		Urinary tract infection	Interstitial nephritis		
Reproductive system and breast disorders					Gynaecomastia
General disorders and administration site conditions	Asthenia Influenza like illness	Chest pain Chills Pyrexia			
Investigations		Increased hepatic enzymes[3]	Weight increased		

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 rabeprazole tablets is first initiated in such patients.

4.9 Overdose

There has been no experience with large overdoses with Rabeprazole.

Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg Rabeprazole once daily (QD). No specific antidote Rabeprazole is known. Rabeprazole is extensively

protein bound and is not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Mechanism of action:

Rabeprazole belongs to a class of anti secretory 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 if regarded as the acid (proton) pump within the parietal cell, Rabeprazole has been characterized as a gastric protonpump inhibitor. Rabeprazole blocks the final step of gastric acid secretion. In gastric parietal cells, Rabeprazole is protonated, accumulates, and is transformed to an active sulfonamide.

5.2 Pharmacokinetic Properties

After oral administration of 20 mg Rabeprazole, peak plasma concentrations (Cm~) of Rabeprazole occur over a range of 2.0 to 5.0 hours (Tm~). There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole is not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

Following oral administration of 20 mg Rabeprazole, it is absorbed and can be detected in plasma by 1 hour. Absolute bioavailability for a 20 mg oral capsule of Rabeprazole is approximately 52%. Rabeprazole is 96.3% bound to human plasma proteins.

Rabeprazole is extensively metabolized. The thioether and sui phone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant anti secretory activity. *In vitro* studies have demonstrated that Rabeprazole is primarily metabolized in the liver by cytochromes P450 3A (sui phone metabolite) and 2C19 (desmethyl Rabeprazole). 90% of the drug is eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites.

The anti-secretory effect begins within one hour alter oral administration of 20 mg Rabeprazole. The median inhibitory effect of Rabeprazole on 24 hour gastric acidity is 88% of maximal alter the first dose. Rabeprazole 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%. This relatively prolonged pharmacodynamic action compared to the short pharmacokinetic half-life (1-2 hours) reflects the sustained inactivation of the H+, K+ATPase.

5.3 Preclinical safety Data

SPECIAL POPULATIONS:
Geriatric: Reported data from clinical studies in healthy elderly subjects indicates that AUC values are approximately doubled and Cm~ increased by 60 % compared to values in a parallel younger control group. There was no evidence of drug accumulation alter once daily dosing.
Pediatric: The pharmacokinetics of Rabeprazole in pediatrics has not been studied.
Gender and race: In analysis of body mass and weight, Rabeprazole pharmacokinetics showed no clinically significant differences between male and female volunteers.
Renal disease: No clinically significant difference was observed in the pharmacokinetics of Rabeprazole between healthy volunteers and patients requiring maintenance haemodialysis.
Hepatic disease: Reported data from single dose clinical study indicates that AUC & elimination half-lives are doubled in patients with mild to moderate liver cirrhosis as compared to healthy volunteers. No information exists on Rabeprazole disposition in patients with severe hepatic impairment.

6. Pharmaceutical Particulars

6.1 List of Excipients

Non Pareil Seeds 16 – 18 # MgCO3-HPMC coated, Hypromellose (E15), Sodium Hydroxide, Light Magnesium Carbonate, Purified Talc, Methacrylic Acid Copolymer dispersion (Drug L 30 D), Macrogol (PEG -6000), Titanium Dioxide, Ferric Oxide (Red), Ferric Oxide (Black),

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 months from date of manufacture.

6.4 Storage

Keep out of reach of children; Protect form light and moisture; Store below 25°C in a dry place.

6.5 Nature and Contents of Container

30 capsules (3 x l0's) in a box and 10x10's in a box

6.6 Special precautions for disposal and other handling

No special requirements for disposal

7. Marketing Authorization Holder: MEGA LIFESCIENCES (AUSTRALIA) PTY. LTD

8. Marketing Authorization Numbers:

9. Date of first authorization / renewal of the authorization:

Date of first authorization: April 2016

10. Date of revision of the text: April 2019

11. Dosimetry (If Applicable)--NA

12. Instructions for Preparation of Radiopharmaceuticals (If Applicable)—NA

1.6.2 Container labeling

Unit Carton
Please refer section 1.5.4

Blister/ Foil
Please refer section 1.5.4

Label
Not Applicable