Professional Information

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

BAPREZ OTC (Enteric coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BAPREZ OTC: Each enteric-coated tablet contains 10 mg rabeprazole sodium equivalent to 9,42 mg rabeprazole

BAPREZ OTC: Contains 5 mg Mannitol per tablet

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

BAPREZ OTC tablets:

Yellow coloured, circular shaped biconvex coated tablets imprinted with ‘R’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Temporary short term relief of heartburn and hyperacidity.

4.2 Posology and method of administration

Posology

Adults/elderly:

The recommended dose is 10 mg (one tablet) daily, for a maximum treatment period of 14 days.

The duration of treatment is up to 2 weeks. Once complete relief of symptoms has occurred, treatment should be discontinued.

If no symptom relief is obtained within 14 days of continuous treatment, the patient is instructed to consult a doctor.

Special Populations

Renal and hepatic impairment

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

Caution is however advised when BAPREZ OTC tablets is first initiated in patients with severe hepatic dysfunction, (see section 4.8).

Paediatric population

BAPREZ OTC tablets are not recommended for use in children, as there is no experience of its use in this group.

Method of Administration

Oral use

BAPREZ OTC 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 BAPREZ OTC tablets should not be chewed or crushed, but should be swallowed whole.

4.3 Contraindications

- Patients with known hypersensitivity to rabeprazole sodium, substituted benzimidazoles or to any excipient used in the formulation (see section 6.1)
- Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Pre-existing malignancy:

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 with severe hepatic dysfunction:

Exercise caution when treatment with rabeprazole is first initiated in patients with severe hepatic dysfunction.

Hepatic enzyme abnormalities have been reported in clinical studies. In the majority of reported cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

Renal failure:

There is an increased risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors which may progress to chronic renal inflammation and renal failure as it is not necessarily reversed when treatment is discontinued.

Hypomagnesaemia:

Severe hypomagnesaemia, symptomatic and asymptomatic, has been reported in patients treated with rabeprazole for at least three months, and in most cases after a year of therapy. Serious adverse events include tetany, dysrhythmias, fatigue, delirium, dizziness and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of rabeprazole. For patients expected to be

on prolonged treatment or who take rabeprazole with medications such as digoxin or medicines that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of rabeprazole treatment and periodically thereafter (see section 4.8).

Fractures:

Rabeprazole therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine, predominantly in older people or in presence of other recognised risk factors. Proton pump inhibitors (PPIs) may increase the overall risk of fracture by 10–40 %. The risk of fracture was reported to be increased in patients who received high-dose, and long-term rabeprazole therapy (a year or longer) (see section 4.8).

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.

Concomitant use of rabeprazole with methotrexate:

The reported literature suggests that concomitant use of rabeprazole with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate-related toxicities. In high-dose methotrexate administration, a temporary withdrawal of rabeprazole may be considered in some patients (see section 4.5).

Gastrointestinal infections:

Treatment with rabeprazole may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile, Campylobacter* and *Salmonella* (see section 5.1).

Influence on vitamin B12 absorption

Rabeprazole sodium, 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 reported to be 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. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPIs.

Co-administration of atazanavir with rabeprazole is not recommended (see section 4.5)

Patients on long-term treatment (particularly those treated for more than 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.

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.

Interference with laboratory tests:

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, rabeprazole treatment should be stopped for at least 5 days before CgA measurements. 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 Interaction with other medicines and other forms of interaction

Cytochrome P450 system:

Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic metabolizing system. Studies in healthy subjects have reported that rabeprazole sodium does not have clinically significant interactions with other medicines metabolised by the CYP450 system, such as warfarin, phenytoin, theophylline or diazepam.

Interactions due to inhibition of gastric acid secretion:

Rabeprazole sodium produces a profound and long-lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur; therefore the potential for such interaction has been reported. Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal levels and a 22 % increase in trough digoxin levels in normal subjects. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when such medicines are taken concomitantly with rabeprazole.

Antacids:

In reported clinical studies, antacids were used concomitantly with the administration of rabeprazole and, in a specific interaction study, no interaction with liquid antacids was reported.

Ciclosporin:

The reported in vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4). The reported studies suggest a low interaction potential; however the effect on ciclosporin metabolism is similar to that reported for other proton pump inhibitors.

Atazanavir:

It has been reported that co-administration of atazanavir 300 mg/ritonavir 100 mg or atazanavir 400 mg with other proton pump inhibitors (PPIs) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH

dependent. Although not reported, similar results are expected with rabeprazole.

Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir (See section 4.4).

Methotrexate

Concomitant administration of rabeprazole 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 interaction studies of methotrexate with rabeprazole have been reported.

Food

No clinically relevant interaction with food has been reported.

4.6. Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been reported.

Pregnancy

Rabeprazole is contraindicated during pregnancy (see section 4.3).

Breastfeeding

Excretion of rabeprazole sodium in human breast milk has not been reported. No studies in breast-feeding women have been reported. Rabeprazole sodium is reported to be excreted in rat mammary secretions. Therefore mothers on treatment with rabeprazole should not breastfeed their babies (See section 4.3).

Fertility

No evidence of impaired fertility or harm to the foetus due to rabeprazole sodium has been reported in rats and rabbits, although low foeto-placental transfer has been reported in rats.

4.7. Effects on ability to drive and use machines

Based on the pharmacodynamic properties and the reported adverse events profile, it is unlikely that rabeprazole would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, or dizziness it is recommended that driving and operating complex machinery be avoided (see section 5.1 and 4.8).

4.8. Undesirable effects

Summary of the safety profile

The most common adverse events, reported with rabeprazole, were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth.

Tabulated list of adverse reactions

The following adverse events have been reported from clinical studies and post-marketing experience and are presented by system organ class and frequency.

Table 1: Tabulated summary of adverse reactions

System Organ Class	Frequent	Less frequent	Frequency not known (cannot be estimated from available data)
Infections and infestations	Infection, including *Salmonella*		
Blood and the lymphatic system disorders		Neutropenia Leucopenia Thrombocytopenia Leucocytosis	
Immune system disorders		Hypersensitivity (for example facial	

		swelling, hypotension and dyspnoea)*	
Metabolism and nutrition disorders		Anorexia	Hyponatremia Hypomagnesaemia
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 ~~Gastric glandular cysts~~	Microscopic colitis
Hepato-biliary disorders		Hepatitis Jaundice Hepatic encephalopathy**	

Signed: PM

Skin and subcutaneous tissue disorders		Rash Erythema* Pruritus Sweating Bullous reactions* Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	Subacute cutaneous lupus erythematosus
Musculoskeletal connective tissue and bone disorders	Non-specific pain/ Back pain	Myalgia Leg cramps Arthralgia Fracture of the hip, wrist or spine	
Renal and urinary disorders		Urinary tract infection Interstitial nephritis	
Reproductive system and breast disorders			Gynaecomastia
General disorders and administration site conditions	Asthenia Flu-like syndrome	Chest pain Chills Fever	
Investigations		Increased hepatic enzymes** Weight gain	

* Erythema, bullous reactions and hypersensitivity reactions have been reported to usually resolve after discontinuation of therapy.

** Hepatic encephalopathy has been reported in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with rabeprazole is first initiated in such patients.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

The reported experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not been reported to exceed 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, similar to the known adverse event profile, and usually reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is, therefore, not readily dialysable. Treatment should be supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A11.4.3 Medicines acting on gastro-intestinal tract.

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 is a gastric proton-pump inhibitor, blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies reported that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Anti-secretory Activity:

After oral administration of a 20 mg dose of rabeprazole sodium the onset of the anti-secretory effect has been reported to occur 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 have been reported to be 69 % and 82 % respectively and the duration of inhibition has been reported to last up to 48 hours. This duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding to the parietal H+/K+- ATPase enzyme. 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 medicine is discontinued, secretory activity normalises over 2 to 3 days.

Serum Gastrin Effects:

Serum gastrin levels have been reported to increase during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion in patients treated once daily with 10 or 20 mg rabeprazole sodium, for up to 24 months duration. Gastrin values have been reported to return to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Rabeprazole sodium is not reported to have clinically significant interactions with amoxicillin in healthy subjects. Rabeprazole sodium does not reportedly influence plasma concentrations of amoxicillin or clarithromycin adversely when co-administered for the purpose of eradicating upper gastrointestinal H. pylori infection.

5.2. Pharmacokinetic properties

Absorption

Rabeprazole sodium is acid-labile, and is therefore administered orally as an enteric-coated (gastro-resistant) tablet formulation. Absorption of rabeprazole sodium therefore begins only after the tablet leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3,5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium 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 is not reported to increase with repeat administration. In healthy subjects the plasma half-life is reported to be approximately one hour (range 0,7 to 1,5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. In patients with chronic hepatic disease, the AUC has been reported to double compare to healthy volunteers, reflecting a decreased first-pass effect, and the plasma half-life increased 2-3 fold.

Distribution

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

Biotransformation

The main plasma metabolites are thioether (M1) and carboxylic acid (M6). Minor metabolites observed at lower levels include sulphone (M2), desmethyl-thioether (M4) and

mercapturic acid conjugate (M5). Only the desmethyl metabolite (M3) has a small amount of antisecretory activity, but it is not present in plasma.

Elimination

Excretion is mainly urinary (90 %), with no unchanged active excreted in the urine. The rest of the metabolites are excreted via the faeces. Total recovery was 99,8 % implying a low biliary excretion of the metabolites of rabeprazole sodium.

Special populations

In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 ml/min/1,73 m2), the disposition of rabeprazole sodium was reported to be very similar to that in healthy volunteers.

Elimination of rabeprazole sodium was reported to somewhat decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled, the Cmax increased by 60 % as compared to young healthy volunteers. However there was no reported evidence of rabeprazole sodium accumulation.

5.3 Preclinical safety data

Non-clinical effects were reported only at exposures sufficiently in excess of the maximum human exposure that make concerns for human safety negligible in respect of animal data.

Reported studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were reported to be positive, but in vivo micronucleus and in vivo and in vitro DNA repair tests were reported to be negative. Carcinogenicity studies reported no special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol,

Heavy Magnesium Oxide,

Low-substituted Hydroxypropyl Cellulose,

Hydroxypropyl Cellulose (L),

Magnesium Stearate,

Ethyl Cellulose,

Light Magnesium Oxide,

Diacetylated Monoglycerides,

Talc,

Titanium Dioxide,

Iron Oxide (Yellow),

Hypromellose Phthalate,

Opacode S-1-1666 red

Composition of Opacode S-1-1666 red:

Shellac,

Allura Red AC Aluminium Lake,

N-Butyl Alcohol,

Propylene Glycol,

Titanium Dioxide,

SDA 3A Alcohol 27CFR (Ethanol, Methanol)

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

36 Months

6.4 Special precautions for storage

Store at or below 25ºC. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Desiccant embedded cold form blisters.

Packed in 7 and 14 blister packs.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (PTY) LTD

14 Lautre Road,

Stormill, Ext.1, Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER

48/11.4.3/1095

9. DATE OF FIRST AUTHORISATION

07 June 2022

10. DATE OF REVISION OF THE TEXT

06 August 2025