Professional Information

SCHEDULING STATUS
S4

1. NAME OF THE MEDICINE
BAPREZ 10 EC (Enteric coated tablets)
BAPREZ 20 EC (Enteric coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
BAPREZ 10 EC: Each enteric-coated tablet contains 10 mg rabeprazole sodium equivalent to 9,42 mg rabeprazole

BAPREZ 20 EC: Each enteric coated tablet contains 20 mg rabeprazole sodium equivalent to 18,85 mg rabeprazole

BAPREZ 10 EC: Contains 5 mg mannitol per tablet
BAPREZ 20 EC: Contains 10 mg mannitol per tablet

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

BAPREZ 10 EC tablets:
Yellow coloured, circular shaped biconvex coated tablets imprinted with 'R' on one side and plain on the other side.

BAPREZ 20 EC tablets:
Yellow coloured, circular shaped biconvex coated tablets imprinted with 'RA' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
BAPREZ tablets are indicated for the treatment of:

- Active duodenal ulcer.
- Active benign gastric ulcer.
- Symptomatic erosive or ulcerative gastro-oesophageal reflux disease (GORD).
- Maintenance treatment of healed erosive or ulcerative GORD. Efficacy has not been demonstrated for periods exceeding 12 months.
- Symptomatic treatment of gastro-oesophageal reflux disease (GORD).
- Zollinger-Ellison Syndrome and other pathological hypersecretory conditions.
- H. Pylori-positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics.

4.2 Posology and method of administration

Posology

Adults/elderly:

Active Duodenal Ulcer and Active Benign Gastric Ulcer:
20 mg To be taken once daily in the morning.
Most patients with active duodenal ulcer heal within four weeks. However, 2 % of patients may require an additional four weeks of therapy to achieve healing.
Some patients with active duodenal ulcer may respond to one 10 mg tablet to be taken once daily in the morning.
Most patients with active benign gastric ulcer heal within six weeks. However 9 % of patients may require an additional six weeks of therapy to achieve healing.

Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD):
20 mg to be taken once daily for four to eight weeks.
Gastro-Oesophageal Reflux Long – term Management (GORD Maintenance):
For long-term management up to 12 months, a maintenance dose of BAPREZ 10 EC mg or 20 mg tablets once daily can be used. Some patients may respond to a maintenance dose of 10 mg/day.
Symptomatic treatment of gastro-oesophageal reflux disease (symptomatic GORD):
10 mg once daily in patients without oesophagitis. If symptom control has not been achieved after 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.
Zollinger-Ellison Syndrome and other pathological hypersecretory conditions:
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.
Eradication of H. Pylori:
BAPREZ tablets are indicated for H. Pylori-positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics.

Special Populations

Renal and hepatic impairment

No dosage adjustment is necessary for patients with renal or hepatic impairment. Caution is however advised when BAPREZ tablets is first initiated in patients with severe hepatic dysfunction, (see section 4.8).

Paediatric population

BAPREZ 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 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 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. Severe hypomagnesaemia can correlate with hypocalcaemia and may also be associated with hypokalaemia. 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 Hypocalcaemia Hypokalemia 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**	
Skin and subcutaneous tissue disorders		Rash Erythema* Pruritus Sweating Bullous reactions* Erythema multiforme, toxic epidermal necrolysis (TEN),	Subacute cutaneous lupus erythematosus

Signed: 07/06/2022

		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	
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 asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reaction Reporting form', found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/index/8

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 compared 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, 10, 28 and 30 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
48/11.4.3/1096

9. DATE OF FIRST AUTHORISATION

07 June 2022

10. DATE OF REVISION OF THE TEXT

Signed: 07/06/2022

Professionele Inligting

SKEDULERINGSTATUS
S4

1. NAAM VAN DIE MEDISYNE
BAPREZ 10 EC (Enteriesbedekte tablette)
BAPREZ 20 EC (Enteriesbedekte tablette)

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
BAPREZ 10 EC: Elke enteriesbedekte tablet bevat 10 mg natriumrabeprasool gelykstaande aan 9,42 mg rabeprasool.

BAPREZ 20 EC: Elke enteriesbedekte tablet bevat 20 mg natriumrabeprasool gelykstaande aan 18,85 mg rabeprasool.

BAPREZ 10 EC: Bevat 5 mg mannitol per tablet.
BAPREZ 20 EC: Bevat 10 mg mannitol per tablet.

Vir die volledige lys van hulpstowwe, sien afdeling 6.1.

3. FARMASEUTIESE VORM

BAPREZ 10 EC tablette:
Geel, ronde, bikonvekse, bedekte tablette met ‘R’ aan die een kant ingepers en glad aan die ander kant.

BAPREZ 20 EC tablette:
Geel, ronde, bikonvekse, bedekte tablette met ‘RA’ aan die een kant ingepers en glad aan die ander kant.

4. KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

BAPREZ tablette word aangedui vir die behandeling van:
- Aktiewe duodenale ulkus.
- Aktiewe benigne gastriese ulkus.
- Simptomatiese eroderende of ulseratiewe gastro-esofageale reflukssiekte (GERS).
- Instandhoudingsbehandeling van eroderende of ulseratiewe GERS wat genees het. Doelmatigheid is nie vir tydperke langer as 12 maande aangetoon nie.
- Simptomatiese behandeling van gastro-esofageale reflukssiekte (GERS).
- Zollinger-Ellison-sindroom en ander patologiese hipersekretoriese toestande.
- *H. pylori*-positiewe duodenale ulkusse, as deel van die uitwissingsprogram saam met toepaslike antibiotika.

4.2 Posologie en metode van toediening
Posologie
Volwassenes/bejaarde pasiënte:
Aktiewe duodenale ulkus en aktiewe benigne gastriese ulkus:
20 mg een keer per dag soggens geneem.
By die meeste pasiënte sal die aktiewe duodenale ulkus binne vier weke genees. By 2 % van pasiënte mag ’n bykomende vier weke se terapie egter nodig wees om genesing te bewerkstellig.

Party pasiënte met ’n aktiewe duodenale ulkus mag ’n goeie respons hê op een 10 mg tablet een keer per dag soggens geneem.
Meeste pasiënte met aktiewe benigne gastriese ulkus genees binne ses weke. By 9 % van pasiënte mag ’n bykomende ses weke se terapie egter nodig wees om genesing te bewerkstellig.

Eroderende of ulseratiewe gastro-esofageale reflukssiekte (GERS):
20 mg een keer daagliks vir vier tot agt weke geneem.

Langtermynbeheer van gastro-esofageale refluks (GERS-onderhoud):
Vir langtermynbeheer van tot 12 maande, kan ’n instandhoudingsdosis van **BAPREZ 10 EC** mg of 20 mg tablette een keer daagliks gebruik word. Party pasiënte mag goed op ’n instandhoudingsdosis van 10 mg/dag reageer.

Simptomatiese behandeling van gastro-esofageale reflukssiekte (simptomatiese GERS):
10 mg een keer daagliks by pasiënte sonder esofagitis. Indien die simptome na vier weke nog nie onder beheer is nie, moet die pasiënt verder ondersoek word. Wanneer simptome opgeklaar het, kan latere simptome beheer word met ’n regimen van 10 mg een keer daagliks geneem wanneer nodig.

Zollinger-Ellison-sindroom en ander patologiese hipersekretoriese toestande:
Die aanbevole aanvangsdosis vir volwassenes is 60 mg een keer daagliks. Die dosis kan opwaarts getitreer word tot soveel as 120 mg/dag, gegrond op die individuele pasiënt se behoeftes. Enkeldosisse van tot 100 mg daagliks mag gegee word. Dit mag nodig wees om die dosis van 120 mg te verdeel, deur 60 mg twee keer daagliks te gee. Behandeling behoort aan te gaan vir so lank as wat dit klinies aangedui word.

Uitwissing van H. pylori:
BAPREZ tablette word saam met gepaste antibiotika as deel van die uitwissingsprogram vir *H. pylori*-positiewe duodenale ulkusse aangedui.

Spesiale populasies

Renale en hepatiese belemmering
Dit is nie nodig om die dosis aan te pas vir pasiënte met belemmerde nier- of lewerfunksie nie.
Versigtigheid word aangeraai wanneer **BAPREZ** tablette die eerste keer gebruik word by pasiënte met erge hepatiese disfunksie (sien afdeling 4.8).

Pediatriese populasie
BAPREZ tablette word nie vir gebruik by kinders aanbeveel nie, aangesien daar geen ondervinding is met die gebruik daarvan by hierdie groep nie.

Metode van toediening
Orale gebruik.
BAPREZ tablette behoort soggens geneem te word, voor ete; alhoewel nie aangetoon is dat die tyd van die dag of inname van voedsel enige effek op die aktiwiteit van natriumrabeprasool het nie, sal hierdie regimen dit makliker maak om aan die behandelingsplan te voldoen.
Pasiënte moet gewaarsku word dat die **BAPREZ** tablette nie gekou of fyngedruk moet word nie, maar heel ingesluk moet word.

4.3 Kontra-indikasies

- Pasiënte met bekende hipersensitiwiteit vir natriumrabeprasool, gesubstitueerde bensimidasole of vir enige hulpstof wat in die formulering gebruik word (sien afdeling 6.1).
- Swangerskap en laktasie (sien afdeling 4.6).

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Voorafbestaande kwaadaardigheid:

Simptomatiese respons op natriumrabeprasool-terapie sluit nie die teenwoordigheid van gastriese of esofageale kwaadaardigheid uit nie, gevolglik behoort die moontlikheid van kwaadaardigheid uitgesluit te word voordat met rabeprasool-behandeling begin word.

Pasiënte met erge hepatiese disfunksie:
Omsigtigheid is nodig wanneer behandeling met rabeprasool vir die eerste keer by pasiënte met erge hepatiese disfunksie begin word.
Abnormaliteite van lewerensieme is in kliniese studies gerapporteer. In die meerderheid van gerapporteerde gevalle waar ’n alternatiewe etiologie nie geïdentifiseer kon word nie, was die effekte ongekompliseerd en het opgeklaar na staking van rabeprasool.

Nierversaking:
Protonpompinhibitors gaan gepaard met ’n verhoogde risiko van subkliniese akute of chroniese interstisiële nefritis, wat kan vorder tot chroniese inflammasie van die nier en nierversaking, aangesien dit nie noodwendig omkeer wanneer behandeling gestaak word nie.

Hipomagnesemie:
Erge hipomagnesemie, simptomaties en asimptomaties, is gerapporteer by pasiënte wat vir ten minste drie maande met rabeprasool behandel is, en in die meeste gevalle na ’n jaar se terapie. Ernstige ongunstige effekte sluit in tetanie, disritmie, uitputting, delirium, duiseligheid en toevalle. By die meeste pasiënte was dit nodig om hipomagnesemie te behandel deur magnesium te vervang en rabeprasool te staak. Hipomagnesemie kan ook gekorreleer word met hipokalemie en hipokalsemie. By pasiënte wat verwag word om op langdurige behandeling te wees of wat rabeprasool neem met medikasies soos digoksien of medisynes wat hipomagnesemie (bv. diuretika) mag veroorsaak, kan gesondheidsorgdeskundiges dit oorweeg om magnesiumvlakke voor aanvang van rabeprasool-behandeling en periodies daarna te monitor (sien afdeling 4.8).

Frakture:
Rabeprasool-terapie mag met ’n verhoogde risiko van osteoporose-verwante frakture van die heup, gewrig of ruggraat gepaard gaan, hoofsaaklik by ouer persone of in die teenwoordigheid van ander erkende risikofaktore. Protonpompinhibitors (PPI's) kan die algehele risiko van ’n fraktuur met 10 – 40 % verhoog. Dit is gerapporteer dat die risiko vir fraktuur hoër is by pasiënte wat hoëdosis- en langtermynterapie met rabeprasool ontvang (’n jaar of langer) (sien afdeling 4.8).
Pasiënte met ’n risiko vir osteoporose moet volgens huidige kliniese riglyne behandel word en moet voldoende vitamien D en kalsium inneem.

Gepaardgaande gebruik van rabeprasool met metotreksaat:
Uit literatuur lyk dit asof die gepaardgaande gebruik van rabeprasool met metotreksaat (hoofsaaklik teen hoë dosisse) die serumvlakke van metotreksaat en/of die metaboliet daarvan kan verhoog en verleng, wat moontlik tot toksisiteite verwant aan metotreksaat kan lei. Waar hoë dosisse metotreksaat toegedien word, kan oorweeg word om rabeprasool tydelik by sommige pasiënte te onttrek (sien afdeling 4.5).

Gastro-intestinale infeksies:
Behandeling met rabeprasool kan moontlik die risiko van gastro-intestinale infeksies, soos *Clostridium difficile, Campylobacter* en *Salmonella,* verhoog (sien afdeling 5.1).

Invloed op absorpsie van vitamien B12:
Natriumrabeprasool mag die absorpsie van vitamien B12 (sianokobalamien) weens hipo- of achlorhidrie verlaag. Dit moet in ag geneem word by pasiënte op langtermynterapie met verlaagde liggaamstore of met risikofaktore vir verlaagde absorpsie van vitamien B12 of indien van die onderskeie kliniese simptome waargeneem word.

Subakute kutane lupus eritematose (SKLE): Dit is gerapporteer dat PPI's met baie uitsonderlike gevalle van SKLE geassosieer word. Indien letsels voorkom, veral in dele van die vel wat aan die son blootgestel is, en indien dit met artralgie gepaard gaan, moet die pasiënt dadelik mediese bystand verkry en die gesondheidsorgdeskundige moet oorweeg om rabeprasool te staak. SKLE na vorige behandeling met ’n PPI kan die risiko van SKLE met ander PPI's verhoog.
Gepaardgaande toediening van atasanavir met rabeprasool word nie aanbeveel nie (sien afdeling 4.5)
Pasiënte op langtermynbehandeling (veral die wat vir langer as ’n jaar behandel word) behoort gereeld ondersoek te word.
’n Risiko van kruishipersensitiwiteitsreaksies met ’n ander protonpompinhibitor (PPI) of gesubstitueerde bensimidasole kan nie uitgesluit word nie.
Ná bemarking is bloeddiskrasie (trombositopenie en neutropenie) gerapporteer. In die meerderheid van gevalle waar ’n alternatiewe oorsaak nie geïdentifiseer kan word nie, was die voorvalle ongekompliseerd en het opgeklaar met staking van rabeprasool.
Inmenging met laboratoriumtoetse: Verhoogde vlak van chromogranien A (CgA) mag inmeng met ondersoeke vir neuro-endokriene tumors. Om hierdie inmenging te vermy, moet rabeprasool-behandeling vir ten minste 5 dae voor CgA-bepalings gestaak word. Indien CgA- en gastrienvlakke nie herstel het tot die verwysingsreikwydte na die aanvanklike bepaling nie, moet die metings 14 dae na staking van PPI-behandeling herhaal word.
4.5 Interaksie met ander medisyne en ander vorms van interaksie
Sitochroom P450-stelsel: Natriumrabeprasool word deur die sitochroom P450 (CYP450) hepatiese metaboliserende stelsel gemetaboliseer. Studies by gesonde proefpersone het gerapporteer dat natriumrabeprasool nie klinies beduidende interaksies het met ander medisynes wat deur die CYP450-stelsel gemetaboliseer word nie, soos warfarien, fenitoïen, teofillien of diasepaam.
Interaksies weens onderdrukking van maagsuursekresie: Natriumrabeprasool veroorsaak ’n radikale en langdurige onderdrukking van afskeiding van maagsuur. ’n Interaksie met verbindings waarvan die absorpsie pH-afhanklik is kan voorkom; gevolglik is die potensiaal vir sodanige interaksie gerapporteer. Gepaardgaande toediening van natriumrabeprasool met ketokonasool of itrakonasool kan ’n beduidende afname in die vlakke van teenswammiddels en ’n styging van 22 % in trogvlakke van digoksien by normale proefpersone veroorsaak. Dit mag dus nodig wees om individuele pasiënte te monitor om te bepaal of die dosis aangepas moet word wanneer hierdie medisynes terselfdertyd as rabeprasool geneem word.
Teensuurmiddels: In gerapporteerde kliniese studies is teensuurmiddels gepaardgaande met toediening van rabeprasool gebruik, en in ’n spesifieke interaksiestudie is geen interaksie met vloeibare teensuurmiddels gerapporteer nie.
Siklosporien: Die gerapporteerde *in vitro* studies met menslike lewermikrosome het aangedui dat natriumrabeprasool deur isoënsieme van CYP450 (CYP2C19 en CYP3A4) gemetaboliseer word. Die gerapporteerde studies stel ’n lae interaksiepotensiaal voor; die effek op metabolisme van siklosporien is egter soortgelyk aan dit wat vir ander protonpompinhibitors gerapporteer is.
Atasanavir: Dit is gerapporteer dat gepaardgaande toediening van atasanavir 300 mg/ritonavir 100 mg of atasanavir 400 mg met ander protonpompinhibitors (PPI's) aan gesonde vrywilligers tot

’n substansiële verlaging in atasanavir-blootstelling gelei het. Die absorpsie van atasanavir is pH-afhanklik. Alhoewel dit nie gerapporteer is nie, word soortgelyke resultate met rabeprasool verwag. Gevolglik moet PPI's, insluitende rabeprasool, nie terselfdertyd as atasanavir toegedien word nie (sien afdeling 4.4).

Metotreksaat:
Gepaardgaande toediening van rabeprasool en metotreksaat (hoofsaaklik teen ’n hoë dosis; sien professionele inligting vir metotreksaat) mag die serumvlakke van metotreksaat en/of sy metaboliet hidroksimetotreksaat verhoog en verleng. Geen formele interaksiestudies van metotreksaat met rabeprasool is egter gerapporteer nie.

Voedsel:
Geen klinies relevante interaksie met voedsel is gerapporteer nie.

4.6. Vrugbaarheid, swangerskap en borsvoeding

Veiligheid tydens swangerskap en borsvoeding is nie gerapporteer nie.

Swangerskap
Rabeprasool word teenaangedui tydens swangerskap (sien afdeling 4.3).

Borsvoeding
Dit is nie gerapporteer of natriumrabeprasool in menslike borsmelk uitgeskei word nie. Geen studies by vrouens wat borsvoed is gerapporteer nie. Dit is gerapporteer dat natriumrabeprasool deur rotte in melk uitgeskei word. Gevolglik moet moeders wat behandeling met rabeprasool ontvang nie hul babas borsvoed nie (sien afdeling 4.3).

Vrugbaarheid
Geen bewyse van belemmerde vrugbaarheid of benadeling van die fetus weens natriumrabeprasool is by rotte en konyne gerapporteer nie, alhoewel lae feto-plasentale oordrag by rotte gerapporteer is.

4.7. Uitwerking op die vermoë om te bestuur en masjiene te gebruik

Gegrond op die farmakodinamiese eienskappe en die gerapporteerde profiel van newe-effekte, is dit onwaarskynlik dat rabeprasool belemmering van bestuursvermoë sal veroorsaak of die vermoë om masjinerie te gebruik sal inkort. Indien waaksaamheid egter belemmer word weens slaperigheid of duiseligheid, word aanbeveel dat bestuur en hantering van ingewikkelde masjinerie vermy word (sien afdelings 5.1 en 4.8).

4.8. Ongewenste effekte

Opsomming van die veiligheidsprofiel
Ongunstige reaksies wat die meeste met rabeprasool gerapporteer is, was hoofpyn, diarree, buikpyn, astenie, flatulensie, uitslag en droë mond.

Getabuleerde lys van ongunstige reaksies
Die volgende ongunstige reaksies is gerapporteer uit kliniese studies en ervaring na bemarking, en word volgens stelsel-orgaan-klas en frekwensie aangebied.

Tabel 1: Getabuleerde opsomming van ongunstige reaksies

Stelsel Orgaan Klas	Dikwels	Minder dikwels	Frekwensie onbekend (kan nie uit beskikbare data geskat word nie)
Infeksies en infestasies	Infeksie, insluitende *Salmonella*		

Bloed- en limfstelselversteurings		Neutropenie Leukopenie Trombositopenie Leukositose		
Immuunstelselversteurings		Hipersensitiwiteit (bv. gesigswelling, hipotensie en dispnee)*		
Metabolisme- en voedingsversteurings		Anoreksie	Hiponatremie Hipomagnesemie Hipokalsemie	
Psigiatriese versteurings	Slaaploosheid	Senuweeagtigheid Depressie	Verwardheid	
Senuweestelselversteurings	Hoofpyn Duiseligheid	Slaperigheid		
Oogversteurings		Visuele versteuring		
Vaskulêre versteurings			Perifere edeem	
Respiratoriese, torakale en mediastinale versteurings	Hoes Faringitis Rinitis	Brongitis Sinusitis		
Gastroïntestinale versteurings	Diarree Braking Naarheid Abdominale pyn Hardlywigheid Flatulensie Fundusklierpoliepe (goedaardig)	Dispepsie Droë mond Eruktasie Gastritis Stomatitis Smaakversteuring	Mikroskopiese kolitis	
Hepatobiliêre versteurings		Hepatitis Geelsug		

		Hepatiese enkefalopatie**		
Vel- en subkutaneweefselversteurings		Uitslag Eriteem* Pruritus Sweting Blaasagtige reaksies* Erythema multiforme, toksiese epidermale nekrolise (TEN), Stevens-Johnson-sindroom (SJS)	Subakute kutane lupus eritematose	
Muskuloskeletale, bindweefsel- en skeletbeenversteurings	Niespesifieke pyn/ Rugpyn	Mialgie Beenkrampe Artralgie Fraktuur van die heup, gewrig of ruggraat		
Nier- en urienwegversteurings		Urienweginfeksie Interstisiële nefritis		
Voortplantingstelsel- en borsversteurings			Ginekomastie	
Algemene versteurings en toestande by die plek van toediening	Astenie Griepagtige sindroom	Pyn in die borskas Kouekoors Koors		
Ondersoeke		Styging in hepatiese ensieme** Gewigstoename		

* Dit is gerapporteer dat eriteem, blaasagtige reaksies en hipersensitiwiteitsreaksies gewoonlik opklaar wanneer terapie gestaak word.

** Hepatiese enkefalopatie is by pasiënte met onderliggende sirrose gerapporteer. Die voorskrywer word geadviseer om omsigtigheid te gebruik wanneer behandeling met rabeprasool vir die eerste keer by pasiënte met erge hepatiese disfunksie begin word.

Rapportering van vermoedelike newe-effekte:

Dit is belangrik om vermoedelike newe-effekte wat gesien word nadat die medisyne geregistreer is, te rapporteer. Dit help met volgehoue monitering van die voordeel/risiko-balans van die medisyne. Gesondheidsorgverskaffers moet asseblief enige vermoedelike newe-effekte aan SAHPRA rapporteer via die vorm om ongunstige geneesmiddelreaksies te rapporteer, wat aanlyn by SAHPRA se publikasies beskikbaar is:
https://www.sahpra.org.za/Publications/index/8

4.9 Oordosering

Tot op hede is ondervinding beperk met doelbewuste of toevallige oordosering. Die maksimum vasgestelde blootstelling het nie 60 mg twee keer daagliks, of 160 mg een keer per dag oorskry nie. Effekte is oor die algemeen minimaal, soortgelyk aan die bekende profiel van ongunstige effekte, en gewoonlik omkeerbaar sonder verdere mediese ingryping. Daar is geen spesifieke teenmiddel bekend nie. Natriumrabeprasool is breedvoerig proteïengebonde, en is gevolglik nie geredelik dialiseerbaar nie. Behandeling moet ondersteunend en simptomaties wees.

5. FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

A11.4.3 Medisynes met uitwerking op gastro-intestinale weg.
Farmakoterapeutiese groep: Spysverteringskanaal en metabolisme, Medisynes vir peptiese ulkus en gastro-esofageale reflukssiekte (GERS), PPI's, ATC-kode: A02B C04.

Meganisme van werking

Natriumrabeprasool is ’n gastriese protonpompinhibitor, wat die finale stap van suurproduksie blokkeer. Hierdie effek is dosisverwant en lei tot onderdrukking van sowel basale as gestimuleerde suurafskeiding, ongeag van die stimulus. In dierestudies is gesien dat natriumrabeprasool na toediening vinnig uit beide plasma en gastriese mukosa verdwyn.

Antisekretoriese aktiwiteit:

Ná orale toediening van ’n 20 mg dosis van natriumrabeprasool is gerapporteer dat die aanvang van die antisekretoriese effek binne een uur is, met die maksimum effek wat binne twee tot vier uur voorkom. Onderdrukking van basale en voedsel-gestimuleerde suurafskeiding 23 uur na die eerste dosis natriumrabeprasool is gerapporteer as 69 % en 82 % onderskeidelik, en die duur van onderdrukking was tot so lank as 48 uur. Hierdie duur van farmakodinamiese werking is veel langer as wat die farmakokinetiese halfleeftyd (ongeveer een uur) sou voorspel. Hierdie effek is waarskynlik weens die voortdurende binding aan die pariëtale H^+/K^+-ATPase-ensiem. Die inhibitoriese effek van natriumrabeprasool op suurafskeiding neem effens toe met herhaalde dosering een keer daagliks, en gelykvlak-inhibisie word na drie dae bereik. Wanneer die medisyne gestaak word, normaliseer die sekretoriese aktiwiteit oor 2 tot 3 dae.

Effekte op serumgastrien:

Dit is gerapporteer dat vlakke van gastrien in die serum toeneem tydens die eerste 2 tot 8 weke, wat die onderdrukkende uitwerking op suurafskeiding reflekteer by pasiënte wat een keer daagliks met 10 mg of 20 mg natriumrabeprasool behandel is, vir tot so lank as 24 maande. Dit is gerapporteer dat gastrienwaardes terugkeer na die vlakke wat dit voor behandeling was, gewoonlik binne 1 tot 2 weke na staking van terapie.

Natriumrabeprasool het nie klinies beduidende interaksies met amoksisillien by gesonde proefpersone nie. Natriumrabeprasool beïnvloed volgens verslae nie die plasmakonsentrasies van amoksisillien of klaritromisien ongunstig wanneer dit gelyktydig toegedien word met die doel om boonste gastro-intestinale *H. pylori*-infeksie uit te wis nie.

5.2. Farmakokinetiese eienskappe

Absorpsie
Natriumrabeprasool is suur-labiel, en gevolglik word dit oraal toegedien in die vorm van ’n enteriesbedekte (gastro-weerstandige) tablet. Absorpsie van natriumrabeprasool begin dus eers nadat die tablet uit die maag uit is. Absorpsie is vinnig, met piek plasmavlakke van natriumrabeprasool wat ongeveer 3,5 uur na ’n 20 mg dosis bereik word. Piek plasmakonsentrasies (C_{maks}) van natriumrabeprasool en AOK is liniêr oor die dosisreikwydte van 10 mg tot 40 mg. Absolute biobeskikbaarheid van ’n orale 20 mg dosis (in vergelyking met intraveneuse toediening) is ongeveer 52 %, grootliks weens presistemiese metabolisme. Daarby is gerapporteer dat die biobeskikbaarheid nie met herhaalde toediening toeneem nie. By gesonde studiedeelnemers is gerapporteer dat die plasmahalfleeftyd ongeveer een uur is (reikwydte 0,7 tot 1,5 uur), en die totale liggaamsopruiming is na beraming 283 ± 98 ml/min. By pasiënte met chroniese lewersiekte, is gerapporteer dat die AOK verdubbel in vergelyking met gesonde vrywilligers, wat ’n verminderde eerstedeurgangeffek reflekteer, en die plasmahalfleeftyd het 2 tot 3-voudig verhoog.

Verspreiding
Natriumrabeprasool is ongeveer 97 % aan menslike plasmaproteïene gebind.

Biotransformasie
Die belangrikste metaboliete in die plasma is tioëter (M1) en karboksielsuur (M6). Mindere metaboliete wat teen laer vlakke waargeneem is, sluit in sulfoon (M2), desmetiel-tioëter (M4) en merkaptuursuurkonjugaat (M5). Slegs die desmetielmetaboliet (M3) het ’n klein mate van antisekretoriese werking, maar dit is nie in die plasma teenwoordig nie.

Eliminasie
Ekskresie is hoofsaaklik in die urine (90 %), met geen onveranderde aktiewe middel wat in die urine uitgeskei word nie. Die res van die metaboliete word via die feses uitgeskei. Totale herwinning was 99,8 %, wat lae biliêre ekskresie van natriumrabeprasool se metaboliete impliseer.

Spesiale pasiëntpopulasies
By pasiënte met stabiele eindstadium-nierversaking wat instandhoudingshemodialise vereis (kreatinienopruiming ≤ 5 ml/min/1,73 m^2), is gerapporteer dat die disposisie van natriumrabeprasool baie soortgelyk aan dié by gesonde vrywilligers was.

Dit is gerapporteer dat die eliminasie van natriumrabeprasool ietwat minder by bejaarde pasiënte was. Ná 7 dae van daaglikse dosering met 20 mg natriumrabeprasool, het die AOK ongeveer verdubbel en die C_{maks} het met 60 % toegeneem vergeleke met jong

gesonde vrywilligers. Geen bewyse van akkumulasie van natriumrabeprasool is egter gerapporteer nie.

5.3 Prekliniese veiligheidsdata

Niekliniese effekte is slegs gerapporteer by blootstellings voldoende in oormaat van die maksimum menslike blootstelling, wat kommer vir veiligheid by die mens onbeduidend maak ten opsigte van data verkry by diere.

Gerapporteerde studies rakende mutagenisiteit het dubbelsinnige resultate gelewer. Toetse by muis-limfoomsellyne was positief, maar *in vivo* mikronukleus- en *in vivo* en *in vitro* DNA-hersteltoetse was negatief. Karsinogenisiteitstudies het geen spesiale gevaar vir mense gerapporteer nie.

6. FARMASEUTIESE BESONDERHEDE

6.1 Lys van hulpstowwe

Mannitol, swaar magnesiumoksied, laagvervangde hidroksipropielsellulose, hidroksipropielsellulose (L), magnesiumstearaat, etielsellulose, ligte magnesiumoksied, gediasetileerde monogliseriede, talk, titaandioksied, ysteroksied (geel), hipromelloseftalaat, Opacode S-1-1666 rooi.
Samestelling van Opacode S-1-1666 rooi: Skilferlak, Allura Red AC aluminiumlak, *N*-butielalkohol, propileenglikol, titaandioksied, SDA 3A Alkohol 27CFR (etanol, metanol).

6.2 Onverenigbaarhede

Nie van toepassing nie.

6.3 Rakleeftyd

36 maande.

6.4 Spesiale voorsorgmaatreëls vir bewaring

Bewaar by of onder 25 °C. Beskerm teen lig en vog.
HOU BUITE BEREIK VAN KINDERS.

6.5 Aard en inhoud van die houer

Koudgevormde stulpstroke met ingeboude uitdroogmiddel.
Verpak in stulppakke wat 7, 28 of 30 tablette bevat.

6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering

Geen spesiale vereistes nie.

7. HOUER VAN DIE REGISTRASIESERTIFIKAAT

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8. REGISTRASIENOMMERS

48/11.4.3/1095
48/11.4.3/1096

9. DATUM VAN EERSTE MAGTIGING

07 June 2022

10. DATUM VAN HERSIENING VAN DIE TEKS