SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

RAPACID 10 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg omeprazole.
Contains sugar: 54,5 mg sucrose
Contains mannitol: 3,955 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.
RAPACID: Opaque, yellow cap and body, no. 3 hard gelatin capsules, containing off-white (ivory) to cream-white, spherical pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RAPACID is indicated for the temporary, short-term relief of heartburn and hyperacidity.

4.2 Posology and method of administration

RAPACID is recommended to be taken in the morning and swallowed whole with a half glass of liquid. The capsule should not be chewed or crushed.

The recommended dose is one or two 10 mg capsules daily.
The maximum daily dose is 20 mg.
The maximum treatment period is 14 days.
If symptom control has not been achieved after 2 weeks of treatment with 20 mg daily, further investigation is recommended.

Special populations

Elderly population

Dose reductions are not necessary in elderly patients.

Renal impairment

Dose reductions are not necessary in renal impairment.

Hepatic impairment

Bioavailability and plasma half-life of RAPACID are increased in patients with impaired hepatic function, therefore a daily dose of 10 to 20 mg is generally sufficient.

The long-term safety of RAPACID in patients with renal and hepatic impairment has not been established (see section 4.4)

Method of administration
For oral use.

4.3 Contraindications
- Hypersensitivity to omeprazole or to any of the inactive ingredients in RAPACID (see section 6.1).
- Safety in pregnancy and lactation has not been established (see section 4.6).
- RAPACID must not be used concomitantly with atazanavir and nelfinavir (see section 4.5)

4.4 Special warnings and precautions for use
RAPACID is not indicated for mild gastrointestinal complaints such as nervous dyspepsia. Symptomatic response to RAPACID therapy does not preclude the presence of gastric ulcer or malignancy or a malignant disease of the oesophagus. The administration of RAPACID in this situation may delay diagnosis. (see Effects related to acid inhibition)

Hepatic and renal impairment
Hepatic impairment may require a reduction in dose. The long-term safety of RAPACID in patients with renal and/or hepatic impairment has not been established. (see section 4.2).

Clostridium difficile-associated diarrhoea
Proton pump inhibitor (PPI) therapy, including RAPACID, may be associated with an increased risk of *Clostridium difficile*-associated diarrhoea (CDAD). This diagnosis should be considered for diarrhoea that does not improve.
Clostridium difficile (*C. difficile*) is a bacterium that can cause diarrhoea that does not improve. Symptoms include watery stool, abdominal pain and fever, and patients may develop more serious intestinal conditions. The disease can also be spread in hospitals. Factors that may predispose an individual to developing CDAD include advanced age, certain chronic medical conditions and taking broad spectrum antibiotics. Treatment for CDAD includes the replacement of fluids and electrolytes and the use of indicated antibiotics.

Effects related to acid inhibition
During long-term treatment, gastric glandular cysts have been reported with increased frequency. These physiological changes result from pronounced inhibition of gastric acid secretion.

Gastrointestinal infection
Decreased gastric acidity increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with RAPACID may lead to an increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

In the presence of symptoms such as significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, or melaena, and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with RAPACID may alleviate symptoms and delay diagnosis.

Acute or chronic interstitial nephritis
PPIs may trigger acute or chronic interstitial nephritis which is commonly associated with acute kidney injury (AKI) leading to chronic renal inflammation and reduced renal function. The preferred term to describe historical findings of tubular injury being “tubulointerstitial nephritis”. Acute tubulointerstitial nephritis is characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium, leading to acute kidney injury. Tubulointerstitial nephritis may be medicine-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to medicine exposure.

The risk of tubulointerstitial nephritis leading to chronic inflammation and reduced renal function associated with the use of proton pump inhibitors such as omeprazole, is a class effect. Hence, PPIs should be used carefully.
Patients on PPIs should be closely monitored for signs or symptoms of acute interstitial nephritis. These may range from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function e.g. malaise, nausea and anorexia.

Clopidogrel
Omeprazole, as in RAPACID, is a CYP2C19 inhibitor. When starting or ending treatment with RAPACID, the potential for interactions with medicines metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and RAPACID. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of RAPACID and clopidogrel should be avoided (see section 4.5).

Combination with other medicines
Concomitant administration of RAPACID and atazanavir and nelfinavir is not recommended (see sections 4.3 and 4.5).

Absorption of vitamin B12 (Cyanocobalamin)
RAPACID may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo-or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Methotrexate
Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of PPIs, such as omeprazole as in RAPACID, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities (see section 4.5).

Risk of fracture
Proton pump inhibitors, such as RAPACID, 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 to 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.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with PPIs like omeprazole, as in RAPACID, 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 dysrhythmia can occur, but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the omeprazole, as in RAPACID. For patients expected to be on prolonged treatment or who take RAPACID with digoxin or medicines that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting RAPACID treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors, such as RAPACID, 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 provider should consider stopping RAPACID. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported very rarely and rarely, respectively in association with omeprazole, as in RAPACID, treatment.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, RAPACID treatment should be temporarily stopped five 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 proton pump inhibitor treatment.

Long-term treatment
When exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Paediatric population
There is very limited experience with the use of RAPACID in children.

Contains sucrose
RAPACID contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Contains mannitol
RAPACID also contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction
RAPACID is metabolised via the hepatic cytochrome P450 enzyme system, which may affect the metabolism of other medications metabolised by these enzymes when given concomitantly.

Medicines with pH-dependent absorption
The decreased intragastric acidity during treatment with RAPACID might increase or decrease the absorption of active medicines with a gastric pH-dependent absorption.

Nelfinavir, atazanavir
According to studies, the plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with RAPACID. Concomitant administration of RAPACID with atazanavir and nelfinavir is contraindicated (see sections 4.3 and 4.4). Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by ca. 40 % and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75 – 90%. The interaction may also involve CYP2C19 inhibition.
Concomitant administration of omeprazole with atazanavir is not recommended (see section 4.4). Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75 % decrease of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy
volunteers resulted in a decrease of approximately 30 % in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

Digoxin
There is a possible interaction of RAPACID with digoxin and a 10 % increase in digoxin bioavailability may be expected. There may be interactions with other medicines, which are also metabolised via the cytochrome P450 enzyme system. According to studies, digoxin toxicity has been reported. Caution should be exercised when RAPACID is given at high doses in elderly patients. Therapeutic medicine monitoring of digoxin should be reinforced.

Clopidogrel
Pharmacokinetic/pharmacodynamic interaction between omeprazole and clopidogrel results in a decreased exposure to the active metabolite of clopidogrel by an average of 46 % for omeprazole. This leads to a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16 % for omeprazole. The consequence of this would be a reduction in the antiplatelet activity of clopidogrel, which may predispose to an increase in cardiovascular events. Concomitant use of omeprazole, as in RAPACID, and clopidogrel should be avoided.

Other active medicines
The absorption of erlotinib, posaconazole, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.

Medicines metabolised by CYP2C19
The elimination of diazepam, warfarin and phenytoin may be prolonged when RAPACID is given concomitantly. Omeprazole, as in RAPACID is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active medicines also metabolised by CYP2C19 may be decreased and the systemic exposure to these medicines increased. Examples of such medicines are warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin. Monitoring of INR and phenytoin serum levels is recommended and dosage reductions may be necessary when RAPACID is given concomitantly.

Cilostazol
Omeprazole, as in RAPACID given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18 % and 26 % respectively, and one of its active metabolites by 29 % and 69 % respectively.

Phenytoin
Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating RAPACID treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending RAPACID treatment.

Unknown mechanism
Saquinavir
Concomitant administration of RAPACID with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70 % for saquinavir associated with good tolerability in HIV-infected patients.

Tacrolimus
Concomitant administration of RAPACID has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Methotrexate
When given together with proton-pump inhibitors, like RAPACID,
methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of RAPACID should be considered (see section 4.4.).

Effects of other medicines on the pharmacokinetics of RAPACID
Inhibitors CYP2C19 and/or CYP3A4
Since omeprazole, as in RAPACID, is metabolised by CYP2C19 and CYP3A4, medicines known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. Dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Medicines known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.
Omeprazole is also partly metabolised by CYP3A4, but omeprazole does not inhibit this enzyme. Thus, RAPACID does not affect the metabolism of medicines metabolised by CYP3A4, such as ciclosporin, lidocaine/lignocaine, quinidine, oestradiol, erythromycin, and budesonide. There is no evidence of interactions with theophylline, propranolol, metoprolol, amoxicillin piroxicam, diclofenac, naproxen, or antacids, but there may be interactions with other medicine also metabolised via the cytochrome P450 enzyme system.

The absorption of RAPACID is not affected by alcohol or food.

4.6 Fertility, pregnancy and lactation
Pregnancy and lactation
Safety in pregnancy and lactation has not been established (see section 4.3).

Breastfeeding
Omeprazole is excreted in breast milk.

Fertility
Research has shown that animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines
Patients taking RAPACID should exercise caution when driving or using machines as this medicine may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or

machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

The most frequent adverse reactions include headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in association with omeprazole, as in RAPACID, treatment.

b) Tabulated summary of adverse reactions

System Organ Class	Frequent	Less frequent	Frequency not known
Infections and infestations		*Clostridium difficile*-associated diarrheoa (CDAD) (see section 4.4)	
Blood and lymphatic system disorders		Pancytopenia, thrombocytopenia, agranulocytosis and leucopenia	
Immune system disorders		Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock	
Metabolism and nutrition disorders		Hyponatraemia, hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia, hypomagnesaemia may also be associated with hypokalaemia	
Psychiatric disorders		Insomnia, agitation, reversible mental confusion, depression, aggression, hallucinations (predominantly in severely ill patients)	
Nervous system disorders	Headache	Dizziness*, paraesthesia, somnolence, taste disturbance	
Eye disorders		Blurred vision	

Ear and labyrinth disorders		Vertigo	
Respiratory, thoracic and mediastinal disorders		Bronochospasm	
Gastrointestinal disorders	Abdominal pain, constipation, diarrhoea*, flatulence, nausea, vomiting, fundic gland polyps (benign)	Dry mouth, stomatitis, gastrointestinal candidiasis, miscroscopic colitis	
Hepato-biliary disorders		Increased liver enzymes, hepatitis with or without jaundice, hepatic failure and hepatic encephalopathy in patients with existing liver disease	
Skin and subcutaneous tissue disorders		Dermatitis, skin rash*, pruritus*, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, alopecia, erythema multiforme, photosensitivity, bullous eruption, urticaria, acute generalised exanthematous pustulosis (AGEP) drug rash with eosinophilia and systemic symptoms (DRESS)	Subacute cutaneous lupus erythematosus
Musculoskeletal, connective tissue and bone disorders		Arthralgia, arthritic and myalgic symptoms*, muscular weakness, fracture of the hip, wrist or spine	
Renal and urinary disorders		Interstitial nephritis (with possible progression to renal failure)	
Reproductive system and breast disorders		Gynaecomastia	

General disorders and administrative site conditions		Malaise, increased sweating, peripheral oedema	

**Symptoms resolved after discontinuation of therapy*

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 Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
Signs and symptoms
Nausea, vomiting, dizziness, abdominal pain, headache, diarrhoea, blurred vision, confusion, diaphoresis, flushing, malaise, and tachycardia have been reported from overdosage with RAPACID. Also apathy, depression and confusion have been described in single cases.
The symptoms described in connection with omeprazole, as in RAPACID, overdosage have been transient, and no serious outcome due to omeprazole has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses and no specific treatment has been needed. There is no specific antidote for overdose with RAPACID.

Treatment
Treatment is symptomatic and supportive.
Due to extensive protein binding, RAPACID is not readily dialysable. Patients in whom overdose is confirmed or suspected should be referred for medical practitioner/doctor consultation.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A 11.4.3 Medicines acting on the gastrointestinal tract – other
Pharmacotherapeutic group: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), Proton pump inhibitors.
ATC code: A02B C01.

Mechanism of action
Omeprazole reduces gastric acid secretion. It is a specific inhibitor of the gastric proton pump in the parietal cell. It produces reversible control of gastric acid secretion with once daily dosing.
Omeprazole is an inhibitor of the gastric proton pump (H+,K+-ATPase). It inhibits both basal and stimulated gastric acid secretion by parietal cells, whether induced by acetylcholine, gastrin or histamine.
Omeprazole has no effect on acetylcholine, histamine or gastrin receptors.

Effect on gastric acid secretion
Oral dosing with omeprazole once daily provides inhibition of gastric acid secretion with maximum effect being achieved within 4 days of treatment. In duodenal ulcer patients, a mean decrease of approximately 80 % in 24-hour intragastric acidity is then maintained, with the mean decrease in peak acidoutput after pentagastrin stimulation being about 70 %, 24 hours after dosing with omeprazole.

5.2 Pharmacokinetic properties
Orally administered omeprazole is well absorbed but to a variable extent. Absorption of omeprazole takes place in the small intestine and is usually completed within three to six hours. Bioavailability depends on the dose and gastric pH,and may reach 70 % with repeated administration. Food has no influence on the bioavailability of omeprazole. Omeprazole is more than 95 % bound to plasma proteins. Clearance from the circulation is by hepatic metabolism with a plasma half-life of 30 to 90 minutes. Hepatic metabolism occurs primarily via the cytochrome P450 (CYP) isoform (CYP2C19). The inactive metabolites are excreted mainly in the urine (80 %) whilst the remaining 20 % are excreted via the faeces. The average half-life of the terminal phase of the plasma concentration-time curve is approximately 40 minutes. There is no change in plasma half-life during treatment. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) and not to the actual plasma concentration at a given time.

5.3 Preclinical safety data
No information available.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Disodium phosphate
Gelatin
Hypromellose
Macrogol 6000
Maize starch
Mannitol
Methacrylic acid-ethyl acrylate copolymer
Polysorbate 80
Purified Water
Quinoline yellow (E104)
Sodium lauryl sulphate
Sucrose
Talc
Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable.

6.3. Shelf life
36 months.

6.4 Special precautions for use
Store at or below 30 °C.
Store in the original package to protect from moisture.

6.5 Nature and contents of container
RAPACID are packed in 14's and 28's into either aluminium/aluminium thermoformed blister packs or opaque white HDPE piljars (containers) with white polypropylene caps containing a desiccant capsule and sealed with a tamper-evident ring.

6.6 Special precautions for disposal
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand,1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER
A39/11.4.3/0466

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