SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RAPACID MR 10, 10 mg hard gelatine capsules.
RAPACID MR 20, 20 mg hard gelatine capsules.
RAPACID MR 40, 40 mg hard gelatine capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RAPACID MR 10: Each hard gelatine capsule contains 10 mg omeprazole.
Excipient with known effect:

- Contains sugar (sucrose): 5,75 mg per capsule.
- Contains sugar (mannitol): 2,5 mg per capsule.

RAPACID MR 20: Each hard gelatine capsule contains 20 mg omeprazole.
Excipient with known effect:

- Contains sugar (sucrose): 11,49 mg per capsule.
- Contains sugar (mannitol): 5 mg per capsule.

RAPACID MR 40: Each hard gelatine capsule contains 40 mg omeprazole.
Excipient with known effect:

- Contains sugar (sucrose): 22,98 mg per capsule.
- Contains sugar (mannitol): 10 mg per capsule.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatine capsules.
RAPACID MR 10:

- Hard gelatine capsule size “4”, with opaque green cap and opaque white body, containing white to off-white cream spherical regular pellets without detectable defects.

RAPACID MR 20:

- Hard gelatine capsule size “4”, with opaque blue cap and opaque white body, containing white to off-white cream spherical regular pellets without detectable defects.

RAPACID MR 40:

- Hard gelatine capsule size “3”, with opaque white cap and opaque grey body, containing white to off-white cream spherical regular pellets without detectable defects.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

RAPACID MR is indicated for the treatment of duodenal ulcer including prevention of relapse, gastric ulcer, reflux oesophagitis, including long term management of patients with reflux oesophagitis, Zollinger-Ellison Syndrome, and for the symptomatic relief of heartburn in patients with gastroesophageal reflux disease and the short-term relief of functional dyspepsia.

RAPACID MR is indicated for *H. pylori*-positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics.

Treatment of NSAID associated gastric and/or duodenal ulcer and erosions and a reduction of the risk to develop gastric and/or duodenal ulcer/erosions and a risk of reduction for relapse of a previously healed gastric and/or duodenal ulcer/erosions in patients on NSAIDs treatment.

Children
Short term (up to 3 months) treatment of severe ulcerative reflux oesophagitis resistant to previous medical treatment.

4.2 Posology and method of administration
Posology
Adults
Duodenal ulcer
The recommended dosage is 20 mg once daily for two to four weeks.
In some duodenal ulcer patients, refractory to other treatment regimens, 40 mg once daily may be effective.
For the prevention of relapse in patients with duodenal ulcer the recommended dose is 10 mg once daily. If needed the dose can be increased to 20 to 40 mg once daily.
RAPACID MR is indicated for *H. pylori*-positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics.
For NSAID associated duodenal ulcers, see *NSAID associated gastroduodenal lesions*.

Gastric ulcer and reflux oesophagitis
The recommended dosage is 20 mg once daily for four to eight weeks.
In some patients with gastric ulcer or reflux oesophagitis refractory to other treatment regimens, 40 mg once daily may be effective.
For the long-term management of patients with reflux oesophagitis, the recommended dose is 10 mg once daily. If needed the dose can be increased to 20 to 40 mg once daily.
In patients with severe or symptomatic recurrent reflux oesophagitis treatment can be continued with RAPACID MR at a dosage of 20 mg once daily.
For NSAID associated gastric ulcers, see *NSAID associated gastroduodenal lesions*.

NSAID associated gastroduodenal lesions
NSAID associated gastric ulcers, duodenal ulcers or gastroduodenal erosions in patients with or without continued NSAID treatment, the recommended dosage of RAPACID MR is 20 mg once daily.

Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.
For the prevention of NSAID associated gastric ulcers, duodenal ulcers, gastroduodenal erosions and dyspeptic symptoms, the recommended dosage of RAPACID MR is 20 mg once daily.

Symptomatic gastroesophageal reflux disease
The recommended dosage is 20 mg daily. Patients may respond adequately to 10 mg daily, and therefore individual dose adjustment should be considered.
If symptom control has not been achieved after four weeks treatment with 20 mg daily, further investigation is recommended.

Functional dyspepsia
For the relief of symptoms in patients with epigastric pain/discomfort with or without heartburn, the recommended dosage is 20 mg once daily.
Patients may respond adequately to 10 mg daily and therefore this dose could be considered as a starting dose.
If symptom control has not been achieved after 2 weeks treatment with 20 mg daily, further investigation is recommended.

Zollinger-Ellison Syndrome
The recommended initial dosage is 60 mg once daily. The dosage should be adjusted individually, and treatment continued as long as is clinically indicated. Patients with severe disease have been effectively controlled on RAPACID MR with more than 90 % maintained on doses of 20 mg to 120 mg daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

Severe ulcerative reflux oesophagitis in children from one year and older
The recommended dosage regime is:
Weight: 10 to 20 kg: RAPACID MR 10 mg once daily.
> 20 kg: RAPACID MR 20 mg once daily.
If needed, dosage may be increased to 20 mg and 40 mg respectively.

Special populations
Elderly
No dose adjustment is necessary in the elderly.

Impaired renal function
No dose adjustment is required in patients with impaired renal function.

Impaired hepatic function
As bioavailability and plasma half-life of omeprazole are increased in patients with impaired hepatic function, a daily dose of 10 to 20 mg is generally sufficient.

The long-term safety of RAPACID MR in patients with renal and hepatic impairment has not been established.

Paediatric population
There is very limited experience with RAPACID MR in children.

Method of administration
For oral administration.
It is recommended to take RAPACID MR in the morning, swallowed whole with half a glass of water. The capsules must not be chewed or crushed.
For patients with swallowing difficulties, these patients can open the capsule and swallow the contents with half a glass of water or after mixing the contents in half a glass of non-carbonated water or fruit juices. Stir until the contents disintegrate and drink the liquid immediately or within 30 minutes.
Rinse the glass with half a glass of fluid and drink. The content of the capsule must not be chewed or crushed.

4.3 Contraindications
- Hypersensitivity to omeprazole or to any of the excipients listed in section 6.1.
- RAPACID MR like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir (see section 4.5).
- Safety in pregnancy and lactation has not been established.
- Hypersensitivity reactions may include acute interstitial nephritis (see section 4.4).

4.4 Special warnings and precautions for use
- RAPACID MR is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.
- In the presence of any alarm symptom (e.g., significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.
- Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g., virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded.
- RAPACID MR may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.
- RAPACID MR is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with medicines metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.
- Hypomagnesaemia:

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole 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 PPI.

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

- Risk of fractures of the hip, wrist and spine:
  Proton pump inhibitors like omeprazole in RAPACID MR, 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.
- Subacute cutaneous lupus erythematosus (SCLE):
  Proton pump inhibitors like RAPACID MR, 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 omeprazole. 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) including Steven's Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported very rarely and rarely, respectively in association with omeprazole treatment.
- Interference with laboratory tests:
  During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole 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 proton pump inhibitor treatment.
  During long-term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.
  Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing medicines may lead to slightly increased risk of gastrointestinal infections such as

Salmonella and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile.*

- Excipients with known effects:
  RAPACID MR contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
  Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract.
- Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.
- As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.
- PPIs may trigger acute or chronic interstitial nephritis which is commonly associated with acute kidney injury (AKI). Acute interstitial nephritis may occur at any time during PPI treatment and is characterised by an inflammatory reaction with the tubulointerstitial space of the kidney. Hence, PPIs should be administered/used carefully. A delay in diagnosis and continued use of the PPI can lead to chronic renal failure.
  Patients on PPI's 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, anorexia.
  Renal function should be frequently monitored and urine checked for haematuria and/or proteinuria in patients on PPIs. Patients should be advised to report any decrease in urine volumes or if they suspect there is blood in their urine. Treatment with PPIs should be discontinued in patients with acute interstitial nephritis.

During long-term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Sodium
RAPACID MR contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

Mannitol
RAPACID MR contains less than 10 g per capsule, that is to say essentially 'mannitol-free'.

Paediatric population
Some children with chronic illnesses may require long-term treatment although it is not recommended.

4.5 Interactions with other medicines and other forms of interaction
Active substances with pH dependent absorption

The absorption of some medicines may be altered due to the decreased intragastric acidity during treatment with omeprazole.
This might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Nelfinavir, atazanavir
The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.
Concomitant administration of omeprazole with nelfinavir is contraindicated (see section 4.3). 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 to 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 once atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg daily.

Digoxin
Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10 %. Digoxin toxicity has been rarely reported. However, caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic medicine monitoring of digoxin should then be reinforced.

Clopidogrel
Studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46 % and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16 %.
Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged (see section 4.4).

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

Active substances metabolised by CYP2C19

Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such medicines are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol
Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} 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 MR treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending RAPACID MR treatment.

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

Methotrexate
When given together with proton-pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Tacrolimus
Concomitant administration of omeprazole 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.

Effects of other active substances on the pharmacokinetics of omeprazole
Inhibitors CYP2C19 and/or CYP3A4
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances 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. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4

Active substances 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.

There is no evidence of an interaction with theophylline, propranolol, metoprolol, lignocaine, quinidine, amoxicillin, metronidazole, erythromycin, budesonide, piroxicam, diclofenac, naproxen or antacids, but there may be interactions with other medicines also metabolised via the cytochrome P450 enzyme system. The absorption of RAPACID MR is not affected by alcohol or food.

Additional information on special populations
No data available.

Paediatric population
No data available.

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

Breastfeeding
Safety in breastfeeding has not been established (see section 4.3).

Fertility
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
RAPACID MR has a negligible influence on the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machinery.

4.8 Undesirable effects
a. Summary of the safety profile
The most common side effects are headache, abdominal pain, constipation, diarrhoea, flatulence, and nausea/vomiting.

b. Tabulated summary of adverse reactions
Adverse reactions listed below are classified according to frequency and System Organ Class (SOC).

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS

Blood and lymphatic system disorders	Less frequent	Leucopoenia, thrombocytopenia, agranulocytosis, pancytopenia.
Immune system disorders	Less frequent	Hypersensitivity reactions e.g., fever, angioedema, and anaphylactic reaction/shock.
Metabolism and nutrition disorders	Less frequent	Hyponatraemia.
	Frequency unknown	Hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders	Less frequent	Insomnia, agitation, confusion, depression, aggression, hallucinations.
Nervous system disorders	Frequent	Headache.
	Less frequent	Dizziness, paraesthesia, somnolence, taste disturbance.
Eye disorders	Less frequent	Blurred vision.
Ear and labyrinth disorders	Less frequent	Vertigo.
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchospasm.
Gastrointestinal disorders	Frequent	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign).
	Less frequent	Dry mouth, stomatitis, gastrointestinal candidiasis.
	Frequency unknown	Microscopic colitis.
Hepatobiliary disorders	Less frequent	Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease.
Skin and subcutaneous tissue disorders	Less frequent	Dermatitis, pruritus, rash, urticaria, alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN). Acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)
	Frequency unknown	Subacute cutaneous lupus erythematosus (see section 4.4).

Musculoskeletal and connective tissue disorders	Less frequent	Fracture of the hip, wrist or spine (see section 4.4), arthralgia, myalgia, muscular weakness.
Renal and urinary disorders	Less frequent	Interstitial nephritis (with possible progression to renal failure)*
Reproductive system and breast disorders	Less frequent	Gynaecomastia.
General disorders and administration site conditions	Less frequent	Malaise, peripheral oedema, increased sweating.

**post-marketing experience*

d. Paediatric population

It is documented that the safety of omeprazole has been assessed in children aged 0 to 16 years with acid-related disease. There are limited long term safety data for children receiving who received maintenance therapy of omeprazole. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long-term data regarding the effects of omeprazole treatment on puberty and growth.

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. Healthcare professionals 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

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2 400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also, apathy, depression and confusion have been described in single cases.

The symptoms described in connection with omeprazole 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.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A. 11.4.3 Medicines acting on gastro-intestinal tract. Other.
Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors, ATC code: A02BC01.

Mechanism of action
Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.
Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H^+ K^+ -ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.
Omeprazole has no effect on acetylcholine, histamine or gastrin receptors.

Pharmacodynamic effects
All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

Effect on gastric acid secretion
Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80 % in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70 % 24 hours after dosing.
Oral dosing with omeprazole 20 mg maintains an intragastric pH of ≥ 3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the oesophagus in patients with gastro-oesophageal reflux disease.

The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time.
No tachyphylaxis has been observed during treatment with omeprazole.

Effect on H. pylori
H. pylori is associated with peptic ulcer disease, including duodenal and gastric ulcer disease. *H. pylori* is a major factor in the development of gastritis. *H. pylori* together with gastric acid are major factors in the development of peptic ulcer disease. *H. pylori* is a major factor in the of development of atrophic gastritis which is associated with an increased risk developing gastric cancer.

Eradication of *H. pylori* with omeprazole and antimicrobials is associated with, high rates of healing and long-term remission of peptic ulcers.
Dual therapies have been tested and found to be less effective than triple therapies. They could, however, be considered in cases where known hypersensitivity precludes use of any triple combination.

Other effects related to acid inhibition
An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

Paediatric population
In a non-controlled study in children (1 to 16 years of age) with severe reflux esophagitis, omeprazole at doses of 0,7 to 1,4 mg/kg improved esophagitis level in 90 % of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0 to 24 months with clinically diagnosed gastro-oesophageal reflux disease were treated with 0,5; 1,0 or 1,5 mg omeprazole/kg. The frequency of vomiting/ regurgitation episodes decreased by 50 % after 8 weeks of treatment irrespective of the dose.

Eradication of H. pylori in children
A clinical study concluded that omeprazole in combination with two antibiotics (amoxicillin and clarithromycin), was safe and effective in the treatment of *H. pylori* infection in children age 4 years old and above with gastritis. However, there was no evidence of any clinical benefit with respect to dyspeptic symptoms. This study does not support any information for children aged less than 4 years.

5.2 Pharmacokinetic properties
Absorption
Omeprazole is acid labile and are therefore administered orally as enteric-coated granules in capsules or tablets.
Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1 to 2 hours after dose.
Absorption of omeprazole takes place in the small intestine and is usually completed within 3 to 6 hours.
Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40 %. After repeated once-daily administration, the bioavailability increases to about 60 %.

Distribution
The apparent volume of distribution in healthy subjects is approximately 0,3 L/kg body weight. Omeprazole is 97 % plasma protein bound.

Biotransformation
Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part

of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxy omeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.
Approximately 3 % of the Caucasian population and 15 to 20 % of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.

Elimination
The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80 % of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

Linearity/non-linearity
The AUC of omeprazole increases with repeated administration.
This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g., the sulphone).
No metabolite has been found to have any effect on gastric acid secretion.

Special population
Hepatic impairment
The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once daily dosing.

Renal impairment
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Elderly
The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75 to 79 years of age).

Paediatric population
During treatment with the recommended doses to children from the age of 1-year, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content of capsule
Disodium phosphate, anhydrous
Hypromellose Type 2910
Macrogol 6000
Magnesium hydroxide
Mannitol
Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)
Polysorbate 80
Sodium lauryl sulphate
Sodium starch glycolate (Type A)
Sugar spheres (sucrose and maize starch)
Talc
Titanium dioxide
Capsule shell (10 mg)
Brilliant blue FCF - FD&C Blue 1 (E133)
Gelatine
Titanium dioxide (E-171).
Yellow iron oxide (E172)
Capsule shell (20 mg)
Gelatine
Indigotine-FD&C Blue2 (E132)
Titanium Dioxide (E171)
Capsule shell (40 mg)
Black iron oxide
Gelatine
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.2 Incompatibilities

Not applicable

6.4 Special precautions for storage

Bottle: Store at or below 25 °C. Keep the bottle tightly closed in order to protect from moisture.
PVC-PE-PVDC /Alu blisters: Store at or below 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
High density polyethylene (HDPE) bottle with silica gel desiccant container in the cap.

RAPACID MR 10:
Bottles 35 mL: 7; 14; 15; 28; 30; 50; 56; 60 and 90 capsules
Bottles 50 mL: 98; 100 and 120 capsules

RAPACID MR 20:
Bottles 35 mL: 7; 14; 15; 28; 30; 50; 56; 60 to 90 capsules
Bottles 50 mL: 98; 100 and 120 capsules
Bottles 100 mL: 250 capsules
RAPACID MR 40:
Bottles 35 mL: 7; 14; 15; 28; 30; 50; 56 to 60 capsules
Bottles 50 mL: 90 capsules
Bottles 100 mL: 98; 100 and 120 capsules

PVC-PE-PVDC/Aluminium thermoformed blisters. The blister strips will be packed in an outer carton.
Blister packs of 10 hard gelatine capsules: 1 blister, 10 capsules per pack; 2 blisters, 20 capsules per pack; 3 blisters, 30 capsules per pack; 5 blisters, 50 capsules per pack; 6 blisters, 60 capsules per pack; 9 blisters, 90 capsules per pack and 10 blisters, 100 capsules per pack.
Blister packs of 14 hard gelatine capsules: 1 blister, 14 capsules per pack; 2 blisters, 28 capsules per pack; 3 blisters, 42 capsules per pack; 4 blisters, 56 capsules per pack; and 7 blister, 98 capsules per pack.

Not all pack sizes may be marketed.

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(S)
RAPACID MR 10: 56/11.4.3/0913
RAPACID MR 20: 56/11.4.3/0914
RAPACID MR 40: 56/11.4.3/0915

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 March 2024

10. DATE OF REVISION OF THE TEXT

adcock ingram