PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] RIVA-OMEPRAZOLE DR

Omeprazole Magnesium Delayed Release Tablets

Tablets (Delayed-Release), 20 mg Omeprazole (as Omeprazole Magnesium), Oral

Manufacturer's Standard

Proton Pump Inhibitor

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	07/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RIVA-OMEPRAZOLE DR (omeprazole magnesium delayed release tablets) is indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as:

- duodenal ulcer
- gastric ulcer
- NSAID-associated gastric and duodenal ulcers
- reflux esophagitis
- symptomatic gastroesophageal reflux disease (GERD), i.e., heartburn and regurgitation
- dyspepsia*: a complex of symptoms which may be caused by any of the organic diseases listed above, or upon investigation no identifiable organic cause is found (i.e., functional dyspepsia);
- Zollinger-Ellison syndrome (pathological hypersecretory condition)
- eradication of *Helicobacter pylori* (*H. pylori*).

***A working definition of dyspepsia would include the presence of epigastric pain/discomfort, with or without heartburn and regurgitation which may be accompanied by nausea, vomiting, bloating, belching, flatulence, early satiety or post -prandial fullness. Symptoms may occur either during the day or throughout the night.**

RIVA-OMEPRAZOLE DR, in combination with clarithromycin and either amoxicillin or metronidazole, is indicated for the treatment of patients with peptic ulcer disease associated with *Helicobacter pylori* infection.

Eradication of *H. pylori* has been shown to reduce the risk of peptic ulcer recurrence. The optimal timing for eradication therapy in patients whose ulcer is not clinically active (i.e., asymptomatic) remains to be determined.

In dyspeptic patients with an *H. pylori* infection, the concurrent gastritis can be healed with appropriate eradication therapy.

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

- RIVA-OMEPRAZOLE DR is contraindicated in patients who are hypersensitive to omeprazole, substituted benzimidazoles or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING .
- RIVA-OMEPRAZOLE DR is contraindicated with co-administration of rilpivirine due to significant decrease in rilpivirine exposure and loss of therapeutic effect.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- No dose adjustment is required in patients with renal insufficiency, hepatic insufficiency, or in elderly patients. The daily dose should not exceed 20 mg (see 10.3 Pharmacokinetics).
- Concomitant use of omeprazole and clopidogrel should be avoided (see 9.4 Drug-Drug Interactions).
- Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

4.2 Recommended Dose and Dosage Adjustment

Omeprazole magnesium 20 mg tablets and Omeprazole magnesium 20 mg capsules have an equivalent effect on 24-hour intragastric pH (proportion of time with intragastric pH ≥ 4). These data support the conclusion that omeprazole magnesium tablet and the omeprazole magnesium capsule can be used with equal efficacy in the treatment of conditions where a reduction of gastric acid secretion is required.

Duodenal Ulcer

Acute Therapy: The recommended adult oral dose is 20 mg given once daily. Healing usually occurs within 2 weeks. For patients not healed after this initial course of therapy, an additional 2 weeks of treatment is recommended.

Refractory Patients: In patients with duodenal ulcer refractory to other treatment regimens, the recommended adult doses are 20 mg - 40 mg given once daily. Healing is usually achieved within 4 weeks in such patients.

Maintenance Therapy for Duodenal Ulcer: Over 95% of duodenal ulcer patients are *H. pylori*-positive, and should be treated with eradication therapy, as described below. A small percentage of patients who are *H. pylori*-negative will experience a disease recurrence and will require maintenance treatment with an antisecretory agent. The recommended omeprazole magnesium dose is 10 mg* once daily, increased to 20-40 mg once daily as necessary.

*RIVA-OMEPRAZOLE DR is NOT available in 10 mg strength.

Gastric Ulcer

Acute Therapy: The recommended adult dose is 20 mg given once daily. Healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: In patients with benign gastric ulcer refractory to other treatment regimens, the recommended adult dose is 40 mg given once daily. Healing is usually achieved within 8 weeks.

Maintenance Therapy for Gastric Ulcer: About 80% of gastric ulcer patients are *H. pylori*-positive, and should be treated with eradication therapy, as described below. A small percentage of patients who are *H. pylori*-negative will experience a disease recurrence and will require maintenance treatment with an antisecretory agent. The recommended RIVA-OMEPRAZOLE DR dose is 20 mg once daily, increased to 40 mg once daily as necessary.

NSAID-Associated Gastric or Duodenal Ulcers

The issue of whether or not eradication of *H. pylori* in patients with NSAID-associated ulcers might have beneficial preventive effects has not yet been settled.

Acute Therapy: In patients with NSAID-associated gastric or duodenal ulcers, the recommended adult dose is 20 mg given once daily. Symptom resolution is rapid and healing usually occurs within 4 weeks. For those patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Maintenance Therapy: For the prevention of relapse in patients with NSAID-associated gastric or duodenal ulcers, the recommended adult dose is 20 mg given once daily, for up to 6 months.

Dyspepsia

Prior to treating patients presenting with dyspeptic symptoms, it should be determined that these symptoms are originating from the upper gastrointestinal tract. Patients presenting alarm symptoms (see 7 WARNINGS AND PRECAUTIONS), and older patients who are at a greater risk of having a serious organic disease, should be investigated prior to the initiation of therapy. If the dyspeptic symptoms are known to be related to a diagnosis of organic disease, the appropriate treatment regimen listed in the sections above should be employed.

If the dyspeptic symptoms are not known to be related to an organic disease, the recommended daily dose of RIVA-OMEPRAZOLE DR is 20 mg once daily for 4 weeks. If after 2 weeks' treatment the patient does not respond to therapy, or there is an early clinical indication of a lack of efficacy, the patient should be thoroughly investigated in order to rule out organic disease (see 7 WARNINGS AND PRECAUTIONS). If there are indications of a clinical response following the initial 2 weeks of treatment, RIVA-OMEPRAZOLE DR may be continued for an additional 2 weeks. Patients may respond adequately to 10 mg* once daily; therefore, individual dose adjustment may be considered.

Epigastric pain/discomfort (with or without heartburn and regurgitation) as predominant symptoms are likely to respond to acid suppression therapy. In all cases, patients who do not respond to 4 weeks' treatment, or whose symptoms recur shortly after discontinuation of treatment, with RIVA-OMEPRAZOLE DR should be investigated for underlying organic diseases.

*RIVA-OMEPRAZOLE DR is NOT available in 10 mg strength.

***Helicobacter pylori* Associated Peptic Ulcer Disease**

Omeprazole, Amoxicillin and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is RIVA-OMEPRAZOLE DR 20 mg, amoxicillin 1,000 mg and clarithromycin 500 mg, all twice daily for seven days.

Omeprazole, Metronidazole and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is RIVA-OMEPRAZOLE DR 20 mg, metronidazole 500 mg and clarithromycin 250 mg, all twice daily for seven days.

To ensure healing and/or symptom control, further treatment with 20 mg RIVA-OMEPRAZOLE DR once daily for up to three weeks is recommended for patients with active duodenal ulcer, and with 20 – 40 mg RIVA-OMEPRAZOLE DR once daily for up to twelve weeks for patients with active gastric ulcer.

Patient compliance with treatment regimens for the eradication of *H. pylori* has been demonstrated to have a positive effect on eradication outcome. In clinical trials, patients treated with triple-therapy regimens have shown high compliance rates.

Susceptibility testing (MIC values derived from the Agar dilution method) of *H. pylori* to metronidazole and clarithromycin is available for 486 primary isolates from patients with a history of duodenal ulcer in one European study. Resistance to metronidazole (MIC >8 mg/L) was detected in 131 strains (27%), while 9 strains (2%) were resistant to clarithromycin (MIC >1 mg/L). Secondary resistance to metronidazole developed in strains from 4 patients treated with omeprazole/metronidazole /clarithromycin. Similarly, in those patients treated with omeprazole/metronidazole/clarithromycin or omeprazole/amoxicillin/clarithromycin combinations, secondary resistance to clarithromycin developed in strains from 4 patients. For amoxicillin, the MIC values at pre-therapy or post-therapy did not indicate any primary, or the development of secondary, resistance to *H. pylori*.

Reflux Esophagitis

Acute Therapy: The recommended adult dose is 20 mg given once daily. In most patients, healing occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended. Refractory Patients: For patients with reflux esophagitis refractory to other treatment regimens, the recommended adult dose is 40 mg given once daily. Healing is usually achieved within 8 weeks.

Maintenance Therapy for Reflux Esophagitis: For the long-term management of patients with healed reflux esophagitis, 10 mg omeprazole (given as capsules) once daily has been found to be effective in controlled clinical trials of 12 months' duration, and in continuous maintenance treatment, in a limited number of patients, for a period of up to 6 years. Therefore, the recommended adult dose of omeprazole magnesium tablets for maintenance treatment of patients with healed reflux esophagitis is 10 mg* given once daily. In the case of recurrence, the dose can be increased to 20-40 mg once daily.

*RIVA-OMEPRAZOLE DR is NOT available in 10 mg strength.

Symptomatic Gastroesophageal Reflux Disease (i.e., Heartburn and Regurgitation)

The recommended adult dose is 20 mg given once daily. Symptom relief should be rapid. If symptom control is not achieved after 4 weeks, further investigation is recommended. Since some patients respond adequately to 10 mg* given once daily, individual dose adjustment should be considered. For the maintenance of symptom relief in patients with gastroesophageal reflux disease (i.e., heartburn and regurgitation) the recommended adult dose is 10 mg given once daily.

*RIVA-OMEPRAZOLE DR is NOT available in 10 mg strength.

Zollinger-Ellison Syndrome

The dose used in the treatment of Zollinger-Ellison syndrome will vary with the individual patient.

The recommended initial dose is 60 mg, given once daily. More than 90% of patients with the severe form of the disease and inadequate response to other therapies have been adequately controlled with doses of 20-120 mg omeprazole capsules daily. With doses greater than 80 mg, the dose should be divided and given twice daily. Doses should be adjusted to the individual patient's need and should continue as long as clinically indicated. Doses up to 120 mg omeprazole capsules three times daily have been administered.

Special Populations

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

RIVA-OMEPRAZOLE DR should be swallowed whole with sufficient water. RIVA-OMEPRAZOLE DR must not be chewed or crushed.

4.5 Missed Dose

A missed dose should be taken as soon as possible, when noticed within 12 hours. However, if more than 12 hours have passed, the missed dose should be skipped, and the regular dosing schedule should be followed.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

Rare reports have been received of overdosage with omeprazole. Single oral doses of up to 400 mg of omeprazole capsules have not resulted in any severe symptoms, and no specific treatment has been needed. One case report described that a single oral dose (560 mg) of omeprazole was associated with moderate increase of white blood cells, generalized malaise, nausea, vomiting, apathy, confusion, drowsiness, moderate headache, flatulence and abdominal pain. As in all cases where overdosing is suspected, treatment should be supportive and symptomatic. Any unabsorbed material should be removed from the gastrointestinal tract, and the patient should be carefully monitored.

When used in combination with an antibiotic, the Prescribing Information/Product Monograph for that antibiotic should be consulted.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet (Delayed-Release) 20 mg Omeprazole Magnesium 20.64 mg (corresponds to 20 mg Omeprazole/tablet)	Mannitol, microcrystalline cellulose, sodium starch glycolate, hydroxypropyl methylcellulose, talc, sodium stearyl fumarate, methacrylic acid copolymer, polyethylene glycol, titanium dioxide, iron oxide (red & yellow), The imprinting ink consists of: shellac, isopropyl alcohol, iron oxide black, N-butyl alcohol, propylene glycol and ammonium hydroxide.

RIVA-OMEPRAZOLE DR 20 mg is red-brown, circular, biconvex, enteric coated tablets, printed “OM” on one side and plain on the other side.

RIVA-OMEPRAZOLE DR is provided in high-density polyethylene (HDPE) child-resistant cap bottles of 100 and 500.

7 WARNINGS AND PRECAUTIONS

General

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with RIVA-OMEPRAZOLE DR is instituted, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant use of omeprazole and clopidogrel should be avoided. See 9.4 Drug-Drug Interactions.

Antibiotic Combination Therapy

NOTE: When used in combination with amoxicillin, clarithromycin or metronidazole, the Product Monographs for those agents must be consulted and followed.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, which are used together with PPIs for the treatment of *H. pylori*, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *Clostridia*. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Clostridium difficile Associated Diarrhea

Decreased gastric acidity due to any means, including any proton pump inhibitor, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors can lead to an increased risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

An increased risk for *Clostridium difficile* infection (CDI) and *Clostridium difficile* associated diarrhea (CDAD) has been observed in association with PPI use in several observational studies. CDI/CDAD should be considered in the differential diagnosis for diarrhea that does not improve. Additional risk factors for CDI and CDAD include recent hospitalization, the use of antibiotics, old age and the presence of comorbidities.

Patients should be prescribed PPIs at the lowest dose and for the shortest duration required for the condition being treated and be reassessed to ascertain whether continued PPI therapy remains beneficial.

Concomitant use of Proton Pump Inhibitors (PPIs) with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate (see 9.4 Drug-Drug Interactions).

Drug Interactions with Antiretroviral Drugs

PPIs have been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. A change in gastric pH may change the absorption of the antiretroviral drug. Other possible mechanisms are via CYP 2C19.

Rilpivirine: Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see 2 CONTRAINDICATIONS).

Atazanavir and Nelfinavir: Co-administration with atazanavir or nelfinavir is not recommended due to decreased atazanavir and nelfinavir exposure (see the Atazanavir and Nelfinavir Product Monographs). If the combination of RIVA-OMEPRAZOLE DR with atazanavir is judged unavoidable, close clinical monitoring is recommended in combination with the use of 400 mg atazanavir/100 mg ritonavir dose; the dose of RIVA-OMEPRAZOLE DR should not exceed 20 mg daily (see Atazanavir Product Monograph).

Saquinavir: If RIVA-OMEPRAZOLE DR is co-administered with saquinavir/ritonavir, caution and monitoring for potential saquinavir toxicities, including gastrointestinal symptoms, increased triglycerides, deep vein thrombosis and QT prolongation are recommended. Dose reduction of saquinavir should be considered from the safety perspective for individual patients (see Saquinavir Product Monograph).

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY.

Short-term treatment and long-term treatment with omeprazole capsules in a limited number of patients for up to 6 years have not resulted in any significant pathological changes in gastric oxyntic endocrine cells.

Endocrine and Metabolism

Hypomagnesemia, Hypokalemia and Hypocalcemia: The chronic use of PPIs may lead to hypomagnesemia. Moreover, hypokalemia and hypocalcemia have been reported in the literature as accompanying electrolyte disorders.

Cyanocobalamin (Vitamin B12) Deficiency: The prolonged use of PPIs may impair the absorption of protein-bound Vitamin B12 and may contribute to the development of cyanocobalamin (Vitamin B12) deficiency.

Gastrointestinal

Long-term use of omeprazole magnesium is associated with an increased risk of fundic gland polyps especially beyond one year (see 8.5 Post-Market Adverse Reactions). Most fundic gland polyps are asymptomatic. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Immune

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. 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 RIVA-OMEPRAZOLE DR. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs (see 8.5 Post-Market Adverse Reactions).

Musculoskeletal

Bone Fracture: Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis- related fractures should be managed according to established treatment guidelines (see 8.5 Post- Market Adverse Reactions).

Renal

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy. Acute tubulointerstitial nephritis can progress to renal failure. Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated (see 8.5 Post-Market Adverse Reactions).

Reproductive Health: Female and Male Potential

- **Fertility**

  In animal studies, fertility and reproductive performance were not affected (see 16 NON-CLINICAL TOXICOLOGY).

- **Teratogenic Risk**

  There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis (see 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

The safety of omeprazole in pregnancy has not been established. RIVA-OMEPRAZOLE DR should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

7.1.2 Breast-feeding

Omeprazole is secreted in breast milk. RIVA-OMEPRAZOLE DR should not be given to nursing mothers unless its use is considered essential.

7.1.3 Pediatrics

The safety and effectiveness of omeprazole magnesium tablets in children have not yet been established.

7.1.4 Geriatrics

Geriatrics (>71 years of age): Benefits of use of PPIs should be weighed against the increased risk of fractures as patients in this category may already be at high risk for osteoporosis-related fractures. If the use of PPIs is required, they should be managed carefully according to established treatment guidelines (see 4 DOSAGE AND ADMINISTRATION and 8.5 Post-Market Adverse Reactions).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Omeprazole is well tolerated. Most adverse reactions have been mild and transient, and have shown no consistent relationship with treatment. Adverse events have been recorded during controlled clinical investigations in 2,764 patients exposed to omeprazole (data taken from controlled clinical studies with omeprazole capsules) or reported from routine use.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In a controlled clinical trial comparing omeprazole to placebo, the prevalence of adverse events with omeprazole 40 mg once daily was similar to that with placebo. In short-term comparative double-blind studies with histamine H_2-receptor antagonists, there was no significant difference in the prevalence of adverse events between omeprazole capsules and the H_2-receptor antagonists. An extensive evaluation of laboratory variables has not revealed any significant changes during omeprazole treatment which are considered to be clinically important. In two short-term studies (20 mg tablet once daily for a maximum duration of 7 days) in a limited number of patients with symptomatic gastroesophageal reflux disease, the adverse event profile seen with the omeprazole magnesium 20 mg tablet is similar to that seen with the omeprazole magnesium 20 mg capsule.

The following adverse events (at a rate of more than 1%) have been reported in individuals receiving omeprazole capsules in controlled clinical situations: diarrhea (2.8%); headache (2.6%); flatulence (2.3%); abdominal pain (1.7%); constipation (1.3%); and dizziness/vertigo (1.1%).

The following is a list of adverse events reported in clinical trials or reported from routine use. Events are categorized by system organ class proposed by MedDRA in alphabetical order. The following definitions of frequencies are used:

Very common	≥ 1/10 (≥ 10%)
Common	≥ 1/100 and < 1/10 (≥ 1% and < 10%)
Uncommon	≥ 1/1,000 and < 1/100 (≥ 0.1% and < 1%)
Rare	≥ 1/10,000 and < 1/1,000 (≥ 0.01% and < 0.1%)
Very rare	< 1/10,000 (< 0.01%), including isolated reports

Table 2*:* Adverse drug reactions reported in clinical trials or reported from routine use presented by MedDRA System Organ Class and frequency

System Organ Class	**Frequency**	**Adverse Reaction(s)**
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia
Ear and labyrinth disorders	Uncommon	Vertigo
Eye disorders	Rare	Blurred vision
Gastrointestinal disorders	Common	Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence
	Rare	Dry mouth, stomatitis, gastrointestinal candidiasis

System Organ Class	Frequency	Adverse Reaction(s)
General disorders and administration site conditions	Uncommon	Malaise
	Rare	Increased sweating, peripheral edema
Hepatobiliary disorders:	Uncommon	Increased liver enzyme levels
	Rare	Encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice and hepatic failure
Immune system disorders	Rare	Hypersensitive reactions including angioedema, fever and anaphylactic shock
Metabolism and nutrition disorders	Rare	Hyponatremia
	Very rare	Hypomagnesemia (severe hypomagnesemia may result in hypocalcemia, and hypomagnesemia may also result in hypokalemia)
Musculoskeletal and connective tissue disorders	Rare	Arthralgia, muscular weakness and myalgia
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, paresthesia, somnolence
	Rare	Taste disturbances
Psychiatric disorders	Uncommon	Insomnia
	Rare	Reversible mental confusion, agitation, aggression, depression and hallucination occurring predominantly in severely ill patients
Renal and urinary disorders	Rare	Interstitial nephritis
Reproductive system and breast disorders	Rare	Gynecomastia
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Skin and subcutaneous tissue disorders	Uncommon	Rash, dermatitis and/or pruritus, and urticaria
	Rare	Photosensitivity, erythema multiforme, Stevens-Johnsons syndrome, toxic epidermal necrolysis (TEN), alopecia

***H. pylori* Eradication Combination Therapy:** The following adverse events (at a rate of more than 1%) were recorded during controlled clinical trials in 493 patients receiving omeprazole, amoxicillin and clarithromycin: diarrhea (28%), taste disturbances (15%), headache (5%), flatulence (4%), nausea (3%), abdominal pain (2%), ALT increased (1%), epigastric pain (1%), pharyngitis (1%) and glossitis (1%).

The following adverse events (at a rate of more than 1%) were recorded during controlled clinical trials in 494 patients receiving omeprazole, metronidazole and clarithromycin: taste disturbances (14%), diarrhea (13%), headache (6%), ALT increased (6%), flatulence (5%), nausea (5%), AST increased (5%), dyspepsia (3%), dry mouth (2%), dizziness/vertigo (2%), epigastric pain (1%), pharyngitis (1%),eructation (1%) and fatigue (1%).

8.5 Post-Market Adverse Reactions

Gastrointestinal disorders

Withdrawal of long-term PPI therapy can lead to aggravation of acid related symptoms and may result in rebound acid hypersecretion.

There have been post-marketing reports of microscopic colitis and fundic gland polyps (PGPs) (see 7 WARNINGS AND PRECAUTIONS).

Musculoskeletal, connective tissue and bone disorders

Osteoporosis and osteoporosis-related fractures have been reported with multiple daily doses and long-term PPI therapy (see 7 WARNINGS AND PRECAUTIONS).

Renal and urinary disorders

There have been post-marketing reports of tubulointerstitial nephritis (with possible progression to renal failure).

Skin and subcutaneous tissue disorders

There have been post-marketing reports of acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS), subacute cutaneous lupus erythematosus (SCLE) (see 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Rilpivirine: Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see 2 CONTRAINDICATIONS).

9.2 Drug Interactions Overview

The gastric acid suppression during treatment with omeprazole and other proton pump inhibitors might decrease or increase the absorption of drugs with gastric pH dependent absorption. Thus, it can be predicted that the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

Omeprazole is metabolized by the cytochrome P-450 system (CYP), mainly in the liver. The pharmacokinetics of the following drugs, which are also metabolized through the cytochrome P-450 system, have been evaluated during concomitant use of omeprazole capsules in humans: aminopyrine, antipyrine, clopidogrel, diazepam, phenytoin, warfarin (or other vitamin K antagonists), cilostazol (not marketed in Canada), theophylline, voriconazole, digoxin, propranolol, metoprolol, lidocaine, quinidine, ethanol, piroxicam, diclofenac and naproxen.

Omeprazole inhibits CYP 2C19, the major omeprazole metabolizing enzyme, and is partially metabolized by CYP 3A4. Drugs known to inhibit CYP 2C19 or CYP 3A4 or both (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of omeprazole's metabolism. Drugs known to induce CYP 2C19 or CYP 3A4 or both (such as rifampin and St John's Wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

9.3 Drug-Behavioural Interactions

Ethanol: There was no significant effect on the pharmacokinetics of ethanol after omeprazole 20 mg.

Driving and Operating Machinery: RIVA-OMEPRAZOLE DR is not likely to affect the ability to drive or use machines.

9.4 Drug-Drug Interactions

The drugs listed hereinafter are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3: Established or Potential Drug-Drug Interactions

Proper/ Common name	Effect	Clinical comment
Aminopyrine and Antipyrine	After 14 days' administration of 60 mg omeprazole once daily, the clearance of aminopyrine was reduced by 19%; the clearance of antipyrine was reduced by 14%. After 14 days' administration of 30 mg once daily, no significant changes in clearance were noted.	–
Antacids	No interaction with concomitantly administered antacids has been found.	–
Antiretroviral Drugs		
Atazanavir	Concomitant administration of omeprazole (20 or 40 mg once daily) substantially reduced plasma C_{max} and AUC of atazanavir in healthy volunteers administered atazanavir or atazanavir/ritonavir (see atazanavir Product Monograph).	Co-administration of RIVA-OMEPRAZOLE DR with atazanavir is not recommended.
Nelfinavir	Concomitant administration of omeprazole (40 mg once daily) with nelfinavir (1,250 mg twice daily) markedly reduced the AUC and C_{max} for nelfinavir (by 36% and 37%, respectively and its active metabolite M8 (by 92% and 89%, respectively) (see nelfinavir Product Monograph).	Co-administration of RIVA-OMEPRAZOLE DR with nelfinavir is not recommended.
Rilpivirine	Concomitant administration of omeprazole with rilpivirine significantly decreased rilpivirine exposure and resulted in loss of therapeutic effect (see 2 CONTRAINDICATIONS).	Co-administration of RIVA-OMEPRAZOLE DR with rilpivirine is contraindicated.
Saquinavir	Concomitant administration of omeprazole with saquinavir increases saquinavir exposure and thus the risk of saquinavir-related toxicities (see the saquinavir Product Monograph). Concomitant administration of omeprazole (40 mg daily) with saquinavir/ritonavir (1,000/100 mg twice daily) increased saquinavir AUC by 82% and C_{max} by 75%.	Co-administration of RIVA-OMEPRAZOLE DR with saquinavir requires caution and monitoring, along with potential dose reduction of saquinavir.

Proper/ Common name	Effect	Clinical comment
Clopidogrel	Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg once daily, i.e., four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. It is, however, uncertain to what extent this interaction is clinically important. One prospective, randomized (but incomplete) study (in over 3,760 patients comparing placebo with omeprazole 20 mg in patients treated with clopidogrel and ASA) and non-randomized, post-hoc analyses of data from large, prospective, randomized clinical outcome studies (in over 47,000 patients) did not show any evidence of an increased risk for adverse cardiovascular outcome when clopidogrel and PPIs, including omeprazole, were given concomitantly. Results from a number of observational studies are inconsistent with regard to increased risk or no increased risk for CV thromboembolic events when clopidogrel is given together with a PPI. When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects, there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups, likely due to the concomitant administration of low dose ASA (see 7 WARNINGS AND PRECAUTIONS).	Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole magnesium in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of RIVA-OMEPRAZOLE DR and clopidogrel should be discouraged.
Diazepam [a]	Following repeated dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54%. The corresponding decrease after omeprazole 20 mg was 26%.	As RIVA-OMEPRAZOLE DR is metabolized through cytochrome P- 450 2C19, it can alter the metabolism and prolong elimination of diazepam

Proper/ Common name	Effect	Clinical comment
Warfarin (or other vitamin K antagonists) [a]	Concomitant administration of omeprazole 20 mg in healthy subjects had no effect on plasma concentrations of the (S)-enantiomer of warfarin, but caused a slight, though statistically significant increase (12%) in the less potent (R)-enantiomer concentrations. A small but statistically significant increase (11%) in the anticoagulant effect of warfarin was also seen. Concomitant treatment with omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin.	In patients receiving warfarin or other vitamin K antagonists, monitoring of INR (International Normalized Ratio) is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary. As RIVA-OMEPRAZOLE DR is metabolized through cytochrome P- 450 2C19, it can alter the metabolism and prolong elimination of warfarin (R-warfarin).
Phenytoin [a]	Following three weeks' treatment with omeprazole 20 mg once daily, the steady-state plasma levels of phenytoin in epileptic patients already receiving concomitant phenytoin treatment were not significantly affected. Urinary excretion of phenytoin and its main metabolite were also unchanged. After single intravenous and oral doses of omeprazole 40 mg in young, healthy volunteers, the clearance of phenytoin was decreased by 15- 20%, and half-life was prolonged by 20-30%. Following repeated dosing with omeprazole 40 mg once daily, the elimination half-life of phenytoin was increased by 27%. Thus, there appears to be a dose-dependent inhibition of elimination of phenytoin by omeprazole. Results from a range of interaction studies with omeprazole magnesium versus other drugs indicate that omeprazole, 20-40 mg given repeatedly, has no influence on any other clinically relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP 1A2 (caffeine, phenacetin, theophylline), CYP 2C9 (S-warfarin), CYP 2D6 (metoprolol, propranolol), CYP 2E1 (ethanol), and CYP 3A (cyclosporin, lidocaine, quinidine, estradiol).	Patients receiving phenytoin and warfarin (or other vitamin K antagonists) should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with RIVA-OMEPRAZOLE DR. As RIVA-OMEPRAZOLE DR is metabolized through cytochrome P- 450 2C19, it can alter the metabolism and prolong elimination of phenytoin.
Cilostazol [a]	Omeprazole, given in doses of 40 mg to health subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites, 3,4- dihydrocilostazol, by 29% and 69% respectively.	As RIVA-OMEPRAZOLE DR is metabolized through cytochrome P- 450 2C19, it can alter the metabolism and prolong elimination of cilostazol.

Proper/ Common name	Effect	Clinical comment
Digoxin	The absorption of digoxin can increase during treatment with omeprazole and other drugs that reduce gastric acidity. Concomitant treatment with omeprazole (20 mg daily) and digoxin in ten healthy subjects increased the bioavailability of digoxin by an average of 10% (up to 30% in two out of ten subjects).	Caution should be exercised when RIVA-OMEPRAZOLE DR is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.
Lidocaine	No interaction with a single intravenous dose of lidocaine or its active metabolite, MEGX, was found after one week of pre-treatment with omeprazole magnesium 40 mg once daily. There were no interactions between omeprazole and lidocaine or MEGX concerning pharmacokinetic variables.	–
Methotrexate	Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted (see 7 WARNINGS AND PRECAUTIONS).	In high-dose methotrexate administration a temporary withdrawal of RIVA-OMEPRAZOLE DR may need to be considered.
Piroxicam, Diclofenac and Naproxen	There was no significant effect on the steady-state pharmacokinetics of piroxicam, diclofenac, and naproxen following repeated dosing with omeprazole 20 mg in healthy volunteers.	–
Propranolol and Metoprolol	No effects on propranolol kinetics were observed in a steady-state trial with 20 mg of omeprazole daily. Similarly, no effects on steady state plasma levels of metoprolol were observed after concomitant treatment with 40 mg omeprazole daily.	–
Quinidine	After one week of omeprazole 40 mg once daily, no effect was observed on the kinetics or pharmacodynamics of quinidine.	–
Tacrolimus	Although no clinical studies have been undertaken, there is a possibility that the concomitant administration of omeprazole and tacrolimus may increase 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.
Theophylline	No effects on oral or i.v. theophylline kinetics have been observed after repeated once daily doses of 40 mg omeprazole.	–

Proper/ Common name	Effect	Clinical comment
Voriconazole	Concomitant administration of omeprazole and a CYP 2C19 and CYP 3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.	A dose adjustment of RIVA-OMEPRAZOLE DR is not required.

[a] Diazepam, Phenytoin, Warfarin (or other vitamin K antagonists) and Cilostazol (not marketed in Canada)

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

St John's Wort is a strong CYP 3A4 inducer. Co-administration with RIVA-OMEPRAZOLE DR may decrease omeprazole plasma concentrations by increasing omeprazole's rate of metabolism.

9.7 Drug-Laboratory Test Interactions

During treatment with antisecretory drugs, serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. Increased CgA levels may interfere with investigations for neuroendocrine tumors. To avoid this interference, RIVA-OMEPRAZOLE DR treatment should be stopped 14 days before CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Omeprazole inhibits the gastric enzyme H^+, K^+-ATPase (the proton pump) which catalyses the exchange of H^+ and K^+. Omeprazole is effective in the inhibition of both basal acid secretion and stimulated acid secretion. The inhibition is dose-dependent. Daily oral doses of omeprazole 20 mg and higher showed a consistent and effective acid control.

Treatment with omeprazole alone has been shown to suppress, but not eradicate *Helicobacter pylori* (*H. pylori*), a bacterium that is strongly associated with acid peptic disease. Ninety to 100% of patients with duodenal ulcers are infected with this pathogen.

Clinical evidence indicates a synergistic effect between omeprazole and certain antibiotics in achieving eradication of *H. pylori*. Eradication of *H. pylori* is associated with symptom relief, healing of mucosal lesions, decreased rate of duodenal ulcer recurrence and long-term remission of peptic ulcer disease, reducing the need for prolonged anti-secretory therapy.

10.2 Pharmacodynamics

Pharmacotherapeutic group: Proton pump inhibitors, ATC-code: A02BC01

In both normal volunteers and hypersecretors, omeprazole inhibited basal nocturnal and daytime acid secretion as well as meal-, histamine-, and pentagastrin-stimulated secretion (omeprazole capsule data).

Table 4: Percentage inhibition of mean acid output after single oral doses of omeprazole

Stimulus	Type of Subject	Omeprazole Dose (mg)		Time after Dose (h)
		20	80	
Basal	HSu*	33%		1-4
Basal-Nocturnal	DU (rem)**	49%		15-24
Sham Feeding	HSu	23%		1.5-3.5
Betazol	HSu	38%		1-4
Pentagastrin	HSu	36%		1-4
Basal	ZES***		97%	2-3

*healthy subject; ** duodenal ulcer in remission; ***Zollinger-Ellison syndrome

Repeated dosing with omeprazole capsule 20 mg once daily provided rapid inhibition of gastric acid secretion, with the maximum effect achieved within the first 4 days of treatment.

Information from two clinical trials in patients with symptomatic gastroesophageal reflux disease indicates that omeprazole magnesium 20 mg tablets demonstrate a similar effect on 24- hour intragastric pH as omeprazole magnesium 20 mg capsules after repeated dosing.

Table 5: Ratios of the proportion of time during a 24-hour period with pH≥ 4 after repeated dose administration of omeprazole in patients with symptoms of GERD

	Ratios of Proportion of Time with Intragastric pH ≥ 4 (over 24 h) for omeprazole magnesium tablet vs. capsule
Study 1	
20 mg, 6 days	0.99 (95% CI: 0.89 to 1.11)
Study 2	
20 mg, 7 days	1.02 (90% CI: 0.94 to 1.06)

It has also been demonstrated that the omeprazole magnesium delayed release tablet has a similar effect on 24-hour intragastric pH as omeprazole magnesium capsule in patients with DU in remission. Therefore, the clinical efficacy of omeprazole magnesium tablet and omeprazole magnesium delayed release tablet are expected to be similar.

Table 6: Proportion of time during a 24-hour period with intragastric pH ≥ 3 in patients with DU in remission

	Ratio (90% CI) of Proportion of Time with Intragastric pH ≥ 3 (over 24 h) for omeprazole magnesium capsule vs. omeprazole magnesium tablet
Study 3	
20 mg, 7 days	1.07 (0.99 to 1.16)

Other Pharmacodynamic Effects: The effect of omeprazole on various organ systems has been investigated (data taken from clinical studies using omeprazole capsules). No clinically significant effects attributable to the drug could be found for the following parameters: Endocrine: plasma levels of insulin, C-peptide, glucagon, PTH, thyroid hormones or sex hormones, basal levels of cortisol; Cardiovascular: blood pressure, heart rate, electrocardiogram; Renal: renal handling of acid and electrolytes; Hepatic: liver enzymes. However, in some patients receiving omeprazole, elevated concentrations of alkaline phosphatase, S-AST and S-ALT have been reported (see 8 ADVERSE REACTIONS).

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

No clinically significant CNS effects have been recorded.

No clinically significant effects on other organ systems have been noted.

Omeprazole has no effect on acetylcholine or H_2-receptors.

10.3 Pharmacokinetics

Absorption

Omeprazole magnesium tablets are absorbed rapidly. Peak plasma levels occur on average within 2 hours. Food has no effect upon the bioavailability of the tablet (AUC), but results in a 30% decrease in peak plasma concentration. However, given the lack of relationship between the peak concentration and the antisecretory effect of omeprazole, RIVA-OMEPRAZOLE DR may be taken with or without food.

Omeprazole magnesium tablets have been compared to the previously available omeprazole magnesium capsules of corresponding strength with respect to, in terms of plasma AUC and C_{max}, in healthy volunteers.

Table 7: Pharmacokinetic measurements following administration of omeprazole magnesium tablets or omeprazole magnesium capsules, in healthy male volunteers

Dosage	Day	Ratio of AUC values (90% CI)	Ratio of C_{max} values	t_{max}
20 mg	1	1.02 (0.94-1.11)	1.05	Omeprazole magnesium tablet: 1.84 (0.8) capsule: 1.46 (0.6)
20 mg	6	1.06 (0.95-1.17)	1.03	Omeprazole magnesium tablet: 1.83 (0.8) capsule: 1.57 (0.6)
10 mg	1	1.01 (0.92-1.11)	1.00	Omeprazole magnesium tablet: 1.86 (1.1) capsule: 1.74 (0.6)

When omeprazole was administered in combination with amoxicillin and clarithromycin to healthy volunteers, there was no clinically significant change in the bioavailability (AUC, C_{max}) of amoxicillin (ratio of AUC values and 95% CI: 1.10; 1.00-1.22). An increase in the bioavailability (AUC) of omeprazole was noted (2.10; 1.85-2.38) and slight increases were seen in the plasma levels of 14- hydroxyclarithromycin (1.34; 1.15-1.57). The plasma levels of clarithromycin were similar when it was administered alone or in combination with omeprazole and amoxicillin (1.14; 0.95-1.36).

There is no statistically significant change in the bioavailability (AUC, C_{max}) of metronidazole during concomitant treatment with omeprazole, in healthy volunteers. The antisecretory effect of omeprazole is correlated to the area under the plasma concentration versus time curve (AUC), but it is independent of the peak plasma concentration (C_{max}).

Distribution

Omeprazole is 95% bound to plasma proteins.

Metabolism and Elimination

The pharmacokinetics of omeprazole are complex with blood levels increasing more than proportionally with increasing dose (20 to 40 mg), and after repeated administration. These increases are probably the result of saturable first-pass metabolism of omeprazole.

Omeprazole undergoes first-pass metabolism and is completely metabolized by the CYP-450 system (CYP), mainly in the liver, through CYP 2C19 and CYP 3A4. The major part of its metabolism is dependent upon the polymorphically expressed, specific isoform, CYP 2C19 (S-mephenytoin hydroxylase). The remaining part is dependent on another specific isoform, CYP 3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP 2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP 2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP 3A4 substrates.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP 2C19 enzyme, extensive metabolizers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. 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 CYP 2C19 enzyme by omeprazole and/or its metabolites (e.g., the sulphone).

Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Poor metabolizers: Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP 2C19 enzyme and are called poor metabolizers. The absolute bioavailability is about 60% after repeated oral dosing (20 mg capsules). In such individuals the metabolism of omeprazole is expected to be catalyzed by CYP 3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolizers than in subjects having a functional CYP 2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations were also higher, by 3 to 5 times. However, these findings have no implication on dosing of omeprazole magnesium.

Following i.v. administration and oral administration (capsules) of omeprazole, 80% of the dose is recovered as urinary metabolites. The remaining 20% is excreted in the feces. Less than 0.1% of the dose administered is excreted in urine as unchanged drug.

Six urinary metabolites have been detected. The two main metabolites have been identified as hydroxyomeprazole and the corresponding carboxylic acid. Three metabolites have been identified in plasma: the sulphide and sulphone derivatives and hydroxyomeprazole. It is unlikely that these metabolites contribute to inhibition of acid secretion.

Omeprazole magnesium tablets and omeprazole magnesium capsules of corresponding strength have comparable bioavailability, in terms of plasma AUC and C_{max} in healthy volunteers. The 20 mg omeprazole magnesium tablets and the 20 mg capsules have an equivalent pharmacodynamic effect as assessed by the effect on the proportion of time during a 24-hour period in which intragastric pH is ≥ 4 in patients with symptomatic gastroesophageal reflux disease.

Special Populations and Conditions

- Genetic Polymorphism & Ethnic Origin: CYP 450 2C19 is a polymorphic enzyme. This heterogeneity is more pronounced in the Asian population where the proportion of slow metabolizers is higher than in Caucasians. In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians. The half-life of omeprazole in slow metabolizers is about 2.5 hours as compared to approximately 1 hour for rapid metabolizers. It is recommended that Asian populations be closely followed-up, particularly when doses are higher than 20 mg and/or there is concomitant hepatic disease.
- Geriatrics: Elderly subjects showed increased bioavailability (36%), reduced total plasma clearance (to 250 mL/min) and prolonged (50%) elimination half-life (to 1.0 hour) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). The mean urinary excretion of metabolites was 68% of the dose. These changes are consistent with reduction in pre-systemic and systemic elimination, typical in the elderly. The daily dose should, as a rule, not exceed 20 mg in this patient group (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).
- Renal Insufficiency: The pharmacokinetics of omeprazole in patients with impaired renal function was virtually the same as in healthy subjects (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules).
- Hepatic Insufficiency: Patients with impaired liver function showed a 75% increase in bioavailability, reduced total plasma clearance (to 67 mL/min), and a four-fold prolongation of the elimination half-life (to 2.8 hours) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). A dose of 20 mg given once daily to these patients for 4 weeks was well tolerated. Dosage for patients with liver cirrhosis and other liver dysfunction should, as a rule, not exceed 20 mg daily (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

Information on the bioavailability of omeprazole magnesium 20 mg tablet in elderly patients, in patients with hepatic insufficiency, and in patients with renal insufficiency is not currently available.

***Helicobacter pylori* eradication using Omeprazole Triple Therapy**

Ninety-five to 100% of duodenal ulcer and 80% of gastric ulcer patients are *H. pylori*-positive, and should be treated with eradication therapy. Eradication of *H. pylori* is associated with long-term remission of peptic ulcer disease. Long-term treatment of these patients with anti-secretory agents is generally not recommended. Long-term treatment with omeprazole is effective in the prevention of relapse of duodenal or gastric ulcer, as demonstrated in clinical studies in patients with unknown *H. pylori* status, and may be used for the minority of patients who are *H. pylori*-negative.

The bioavailability of amoxicillin was studied during concomitant administration with omeprazole in fasting healthy adult subjects. When a single dose of amoxicillin, 750 mg, was administered to subjects who had received repeated doses of omeprazole 40 mg twice daily for 3 weeks, no significant change in the bioavailability (AUC, C_{max}) of amoxicillin was observed.

Clarithromycin 500 mg three times daily and omeprazole 40 mg capsules once daily were studied following concomitant administration in fasting healthy adult subjects. When clarithromycin was administered with omeprazole, increases in omeprazole half-life and AUC_{0-24} were observed. For all subjects combined, the mean omeprazole AUC_{0-24} was 89% greater and the harmonic mean for omeprazole $t_{1/2}$ was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state C_{max}, C_{min} and AUC_{0-8} of clarithromycin were increased by 10%, 27% and 15%, respectively, over values achieved when clarithromycin was administered with placebo.

11 STORAGE, STABILITY AND DISPOSAL

RIVA-OMEPRAZOLE DR is moisture sensitive.

RIVA-OMEPRAZOLE DR is also provided in HDPE child-resistant cap bottles.

Store in a dry place at controlled room temperature (15-30°C).

Keep this medicine out of reach and sight of children.

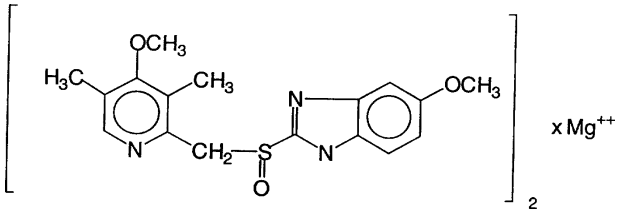
12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	omeprazole magnesium
Chemical name:	Di (5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl}-1H-benzimidazole) magnesium
Structural formula:	
Molecular formula:	$C_{34}H_{36}N_6O_6S_2$ Mg
Molecular mass:	713.1 (anhydrous basis) g/mol
Physiochemical properties:	Omeprazole magnesium is a white to off-white crystalline powder, containing between 2 and 4 waters of hydration. The solubility in water is 0.25 g/L, and the solubility in methanol is 10 g/L. The pKa of the benzimidazole (omeprazole base) is 8.8, and that of the pyridinium ion, 4.0.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indications

Peptic ulcer disease associated with *Heliobacter pylori*

Patients who fail to have their infection eradicated may be considered to have *H. pylori* resistant to the antimicrobials used in the eradication regimen. Therefore, therapy involving alternative effective antimicrobial agents should be considered (if re-treating).

It has been demonstrated that resistance to metronidazole is a negative predictive factor, decreasing the eradication rate of *H. pylori* obtained with triple-therapy (omeprazole, metronidazole and clarithromycin) by 10-20%. The addition of omeprazole to metronidazole and clarithromycin appears to reduce the effect of primary resistance and the development of secondary resistance compared to antimicrobials alone.

Pivotal studies

Four studies on the combination of omeprazole with antimicrobials conducted in patients with *H. pylori* infection and active or inactive peptic ulcer disease are described below.

Efficacy (*H. pylori* eradication rate) in studies 2-4 was analysed according to Intention To Treat (ITT) analysis, which included all patients that actually received at least one dose of therapy and were *H. pylori*-positive. In study 1, the APT (All Patients Treated) method was used instead. This method is defined in a similar way. The results from the studies were also analysed using the Per Protocol (PP)

analyses. In the PP analysis, all study subjects who strictly follows the protocol are included. In studies 3 and 4, only patients with active duodenal (3) and gastric (4) ulcer disease were studied. The influence of *H. pylori* resistance to clarithromycin on the eradication rate was investigated in study 2. In studies 3 and 4, ulcer healing rate as well as relapse rate were studied. Effects of eradication on gastric mucosal morphology was also investigated in these studies.

Table 8: Summary of patient demographics for clinical trials in patients with a history of duodenal ulcer who were *H. pylori*-positive

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)
Study 1 (SH-OMH-0001)	DB, PG	omeprazole 20 mg + amoxicillin 1,000 mg + clarithromycin 500 mg (OAC_{500}), all twice daily for one week	787* 684+ 780++
		omeprazole 20 mg + metronidazole 400 mg + clarithromycin 250 mg (OMC_{250}), all twice daily for one week	
		omeprazole 20 mg + placebo (OP), all twice daily for one week	
Study 2 (SH-OMH-0005)	DB, PG	omeprazole 20 mg + amoxicillin 1,000 mg + clarithromycin 500 mg (OAC_{500}), all twice daily for one week	539* 514** 535++
		omeprazole 20 mg + metronidazole 400 mg + clarithromycin 250 mg (OMC_{250}), all twice daily for one week	
		amoxicillin 1,000 mg + clarithromycin 500 mg (AC), all twice daily for one week	
		metronidazole 400 mg + clarithromycin 250 mg (MC), all twice daily for one week	

* patients randomized; ** patients included in ITT analysis; + patients included in APT analysis; ++ patients eligible for safety analysis; DB = double-blind; PG = parallel groups

Study 1 is a double-blind, randomized, international, multi-center pivotal trial where omeprazole alone and five different seven-days eradication regimens, all containing omeprazole and two antimicrobials were investigated with regard to *H. pylori* eradication rate. One of the treatment arms comprised the combination of omeprazole 20 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid. In another arm, a lower dose of clarithromycin, 250 mg bid was used.

Study 2 is a double-blind, randomized, international multi-center pivotal trial where the importance of omeprazole for the eradication of *H. pylori* in patients with duodenal ulcer disease was investigated. Two combinations of antimicrobials, clarithromycin 500 mg bid plus amoxicillin 1 g bid, and metronidazole 400 mg bid plus clarithromycin 250 mg bid were used alone or together with omeprazole 20 mg bid for seven days.

Table 9: Results of studies in patients with a history of duodenal ulcer who were *H. pylori*-positive

Study #	Primary Endpoints	Treatment	APT or ITT Analysis	PP Analysis
Study 1	Eradication rate	OAC_{500}	96% (95% CI 77-91%)	98%
		OMC_{250}*	95% (95% CI 90-99%)	94%
		OP	1% (95% CI 0-3%)	–
Study 2	Eradication rate	OAC_{500}	94% (95% CI 88-97%)	95%
		OMC_{250}*	87% (95% CI 79-92%)	91%
		AC	26% (95% CI 19-34%)	–
		MC	69% (95% CI 60-77%)	–

95% CI = 95% confidence interval; * 500 mg metronidazole appears to be equivalent to 400 mg with regards to efficacy and safety

Study 1: Patients included in the APT and PP analyses were assessed for *H. pylori* status by UBT pre- and post-treatment, n = 684 (APT analysis).

Study 2: Patients included in the ITT and PP analyses were assessed for *H. pylori* status by UBT and culture pre- and post-treatment, n = 514 (ITT analysis).

Table 10: Summary of patient demographics for clinical trials in patients with active peptic ulcer who were *H. pylori*-positive

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)
Study 3 (SH-OMH-0006)	DB, PG	omeprazole 20 mg + amoxicillin 1,000 mg + clarithromycin 500 mg (OAC_{500}), all twice daily for one week	149* 146** 149++
		omeprazole 20 mg + metronidazole 400 mg + clarithromycin 250 mg (OMC_{250}), all twice daily for one week	
		omeprazole 20 mg + placebo (OP), all twice daily for one week	
Study 4 (SH-OMH-0007)	DB, PG	omeprazole 20 mg + amoxicillin 1,000 mg + clarithromycin 500 mg (OAC_{500}), all twice daily for one week	160* 145** 157++
		omeprazole 20 mg + metronidazole 400 mg + clarithromycin 250 mg (OMC_{250}), all twice daily for one week	
		omeprazole 20 mg + placebo (OP), all twice daily for one week	

* patients randomized; ** patients included in ITT analysis; ++ patients eligible for safety analysis; DB = double-blind; PG = parallel groups

Study 3 is a double-blind, randomized, multi-center pivotal study conducted in Canada. Eradication rates of *H. pylori* (primary objective) in patients with active duodenal ulcers treated with omeprazole alone, or the combination of omeprazole plus clarithromycin with either amoxicillin or metronidazole were compared. Treatment with omeprazole 20 mg od was continued for three weeks after eradication treatment.

Study 4 is a double-blind, randomized, international, multicenter pivotal study with three parallel groups comparing the eradication rates of *H. pylori* (primary objective) in patients with active gastric ulcer. The patients were treated with omeprazole alone, or with omeprazole plus clarithromycin in combination with either amoxicillin or metronidazole. Treatment with omeprazole, 20 mg od continued three weeks further.

Table 11: Results of studies in patients with active peptic ulcer who were *H. pylori*-positive

Study #	**Primary Endpoints**	**Treatment**	**ITT Analysis**	**PP Analysis**	**Ulcer Healing Rate (Post Treatment)**	**Rate of Patients in Remission (6 months after cessation therapy)**
Study 3	Eradication	OAC_{500}	78%	87%	92%	88%
	rate		(95% CI 64-88%)			
		OMC_{250}*	85%	92%	94%	92%
			(95% CI 72-94%)			
		OP	0% (95% CI 0-7%)	–	90%	48%
Study 4	Eradication	OAC_{500}	79%	83%	94%	83%
	rate		(95% CI 65-90%)			
		OMC_{250}*	86%	93%	96%	92%
			(95% CI 73-94%)			
		OP	4%	–	96%	73%
			(95% CI 0-14%)			

95% CI = 95% confidence interval; * 500 mg metronidazole appears to be equivalent to 400 mg with regards to efficacy and safety

Study 3: Patients with duodenal ulcer, included in the ITT analysis, were assessed for *H. pylori* status by UBT and histology pre- and post-treatment, n = 146 (ITT analysis).

Study 4: Patients with gastric ulcer, included in the ITT analysis, were assessed for *H. pylori* status by UBT and histology pre- and post-treatment, n = 145 (ITT analysis).

14.2 Comparative Bioavailability Studies

Fasted Study:

A double blind, randomised, two-treatment, two-sequence, four-period, single oral dose, fully replicated crossover, bioequivalence study of RIVA-OMEPRAZOLE DR, 20 mg (Laboratoire RIVA Inc.) and LOSEC® Delayed Release Tablets, 20 mg (AstraZeneca Canada Inc.) was conducted in thirty-one (31) healthy, adult, Asian male subjects under fasting conditions. A summary of the comparative bioavailability data is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Omeprazole (1 X 20 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h / mL)	907.0 1487.1 (115.8)	953.4 1518.5 (112.8)	95.1	89.4-101.3
AUC_I (ng·h / mL)	920.7 1500.5 (115.3)	966.6 1566.0 (111.1)	95.2	89.5–101.4
C_{max} (ng / mL)	442.6 542.1 (64.5)	481.1 580.5 (61.6)	92.0	84.3-100.4
T_{max}[3] (h)	2.5 (1.3 – 5.5)	2.7 (1.3 – 10.0)		
$T_{½}$[4] (h)	1.1 (64.0)	1.2 (61.4)		

[1] RIVA-OMEPRAZOLE DR (omeprazole magnesium) Delayed Release Tablets, 20 mg (Laboratoire RIVA Inc.)
[2] [Pr] LOSEC® (omeprazole magnesium) Delayed Release Tablets, 20mg (AstraZeneca Canada Inc.)
[3] Expressed as median (range) only
[4] Expressed as the arithmetic mean (CV %) only

Fed Study:

A double blind, randomised, two-treatment, two-sequence, four-period, single oral dose, fully replicated crossover, bioequivalence study of RIVA-OMEPRAZOLE DR, 20 mg (Laboratoire RIVA Inc.) and LOSEC® Delayed Release Tablets, 20 mg (AstraZeneca Canada Inc.) was conducted in twenty-seven (27) healthy, adult, Asian male subjects under high-fat, high-calorie fed conditions. A summary of the comparative bioavailability data is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Omeprazole (1 X 20 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h / mL)	1124.3 2007.7 (108.9)	1076.0 2096.9 (115.5)	104.5	87.9-124.2
AUC_I (ng·h / mL)	1347.0 2266.8 (99.7)[3]	1377.1 2383.4 (104.0)[4]	97.8	88.7–107.9
C_{max} (ng / mL)	511.9 670.4 (67.2)	529.6 707.5 (65.6)	96.6	81.9-114.0
T_{max}[5] (h)	6 (3 – 22)	6 (3 – 22)		
$T_{½}$[6] (h)	1.4 (80.4)[3]	1.4 (82.2)[4]		

[1] RIVA-OMEPRAZOLE DR (omeprazole magnesium) Delayed Release Tablets, 20 mg (Laboratoire RIVA Inc.)
[2] [Pr] LOSEC®(omeprazole magnesium) Delayed Release Tablets, 20 mg (AstraZeneca Canada Inc.)
[3] n = 26 subjects
[4] n = 25 subjects
[5] Expressed as median (range) only
[6] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

Omeprazole magnesium, in combination with appropriate antibiotics, is approved for eradication of *Helicobacter pylori* in the treatment of peptic ulcers.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Single-Dose Toxicity (see Table 12): The highest oral dose (4,000 mg/kg) of non-micronized omeprazole did not cause death in any of the species tested. With micronized omeprazole, suspended in Methocel®, the acute oral LD_{50} was approximately 1,500 mg/kg in mice; in male rats, higher than the maximum dose (5,000 mg/kg); and in female rats, approximately 3,000 mg/kg. As much as 80% of the compound may not have been absorbed due to acid degradation of these single doses in the stomach. Death occurred within 2 days of ingestion and was preceded by reduced motor activity, reduced respiration frequency but increased respiration depth, reduced body temperature, and twitching, tremor or convulsions. The highest oral dose given to dogs (660 mg/kg) caused vomiting within 40-100 minutes of ingestion. The acute intravenous LD_{50} was 83 mg/kg in male mice, and in female mice >100 mg/kg. The corresponding figure in rats was >40 mg/kg. Death occurred within a few minutes of injection, preceded by cyanosis and convulsions.

The oral LD_{50} of omeprazole in male and female rats and mice was greater than 4,000 mg/kg. In dogs, the only sign of acute toxicity was vomiting, which occurred at doses of approximately 600 mg/kg.

Table 12: Single-dose toxicity studies of omeprazole

Species	Sex	Route	LD_{50} (mg/kg)
Mouse	M	p.o.[1]*	> 4,000
	F	p.o.[1]*	> 4,000
Mouse	M	p.o.[1]*	1,520
	F	p.o.[1]*	1,380
Mouse	M	i.v.	83
	F	i.v.	> 100
Rat	M	p.o.[1]*	> 4,000
	F	p.o.[1]*	> 4,000
Rat	M	p.o.[1]*	> 5,010
	F	p.o.[1]*	3,320
Rat	M	i.v.	> 40
	F	i.v.	> 40

[1] suspension of Methocel®, not buffered; * non-micronized test compound

Repeat-Dose Toxicity: The general, long-term toxicity of omeprazole was studied in mice, rats and dogs after oral and intravenous administration. Mice received oral doses of 14-140 mg/kg for up to 18 months, rats 14-400 mg/kg for up to 24 months, and dogs 1-140 mg/kg for up to 12 months. Intravenous omeprazole was given to rats in doses of 2-16 mg/kg for up to one month and to 10 dogs in doses of 1-9 mg/kg for up to one month.

In the dog, a slight to moderate atrophy of the chief cells and rugal hypertrophy were observed. These changes were reversible after treatment cessation.

Following chronic intravenous administration of omeprazole to rats (~1.7-15.5 mg/kg/day) for one month and to dogs (~0.7-8.6 mg/kg/day) for one month, no treatment-related changes were observed.

In the rat, decreased plasma concentrations of triiodothyronine were observed in the two highest groups; TSH increased in the high-dose males. Lower doses had no significant effect. General hypertrophy of the oxyntic mucosa was found; the size of some chief cells was decreased and some granularity was observed. Both the hypertrophy and chief cell changes were reversible.

Carcinogenicity

An 18-month oral study was conducted in mice at doses of 14, 44 and 140 mg/kg/day. No evidence of carcinogenic potential was seen. A 24-month oral study was conducted in rats at doses of 14, 44 and 140 mg/kg/day. No increase in carcinomas was observed in any organ. However, there were dose- and time-dependent increases of tumor-like proliferations in the stomach. Histology showed a continuum from diffuse ECL-cell hyperplasia in the basal region of the gastric glands to less frequent micronoduli and occasional tumor-like proliferations, some extending into the sub-mucosa. The proliferations were classified as gastric carcinoids. The proliferation of ECL-cells and development of carcinoids were more frequent in female rats.

No metastases were identified in any of the animals. Carcinoids have not been observed after long- term administration of omeprazole to mice and dogs.

The rat carcinogenicity study (24 months) revealed a gradual development from gastric ECL-cell hyperplasia to carcinoids at the end of their normal life-span during administration with14-140 mg/kg/day of omeprazole. No metastasis developed. No carcinoids developed during 18 months' high-dose treatment of mice (14-140 mg/kg/day). Similarly, administration of omeprazole up to 28 mg/kg/day in dogs for 7 years did not cause any carcinoids.

The gastric carcinoids in rats were related to sustained hypergastrinemia secondary to acid inhibition and not to omeprazole per se. Similar observations have been made after administration of histamine H_2-receptor blockers and also in partially fundectomized rats.

Genotoxicity

Omeprazole was tested *in vivo* (mouse micronucleus test, chromosome aberration in mice) and *in vitro* (Ames test, mouse lymphoma forward mutation assay), and showed no evidence of a mutagenic effect.

Pharmacodynamics

Omeprazole differs from existing inhibitors of gastric acid secretion such as histamine H_2-receptor antagonists and anticholinergic agents in its ability to directly inhibit the gastric H^+, K^+-ATPase. This enzyme has been identified as the proton pump of the parietal cell.

Omeprazole had a long duration of action in all species studied. Repeated daily doses resulted in a progressive increase in the antisecretory effect during the first 3-5 days of administration. In dogs, a dose of 0.5 mcmol/kg (given as enteric coated granules) inhibited histamine-stimulated gastric acid secretion by about 20% when measured 24 hours after the first dose, and by 60-65% when measured 24 hours after dosing at steady state. Once steady-state conditions were reached (after 3-5 days), acid inhibition remained unchanged, as established in dogs treated for periods of up to one year.

Acid secretion recovers after discontinuation of long-term treatment at the same rate as after a single dose of omeprazole, in parallel with the recovery of H^+, K^+-ATPase activity in the oxyntic mucosa. Whether this recovery reflects de novo synthesis of the H^+, K^+-ATPase molecules or the dissociation of the inhibitor from the enzyme has not yet been established.

Due to the potency and long duration of action of omeprazole, repeated administrations of high doses in the rat resulted in a marked decrease of acid secretion and a secondary hypergastrinemia and hyperplasia of G-cells. In rats, administration of omeprazole 14-140 mg/kg/day resulted in plasma gastrin levels of 1,000-3,000 pg/mL as compared to 150-200 pg/mL in controls. In dogs, high doses of omeprazole (28 mg/kg/day) produced marked hypergastrinemia (1,000-2,000 pg/mL after food intake), as compared to 100-300 pg/mL in controls. However, no hyperplasia of G-cells was evident in this species.

Secondary Pharmacological Effects: Mean arterial blood pressure and heart rate in the anesthetized dog were not affected by omeprazole under various challenges. Circulatory and respiratory functions in the dog were not affected by omeprazole, either at rest or during exercise. Omeprazole had no anticholinergic and no antihistamine (H_2-receptor) activity. In the rat, no effect on basal locomotor activity nor on exploratory activity was recorded, suggesting that omeprazole is devoid of sedative or neuroleptic effects.

Other Interactions: Omeprazole interacts with cytochrome P-450 in the rat liver. Omeprazole prolonged hexobarbital sleeping time by 12%.

Pharmacokinetics

Absorption: Omeprazole is degraded rapidly in acidic gastric juice (rat and dog studies). Absorption is rapid. Peak plasma levels were found within 20 minutes and 1 hour after intra-duodenal and oral administration, respectively, in the dog. The drug has a low oral bioavailability, 5% in unstarved rats and 15-20% in starved male and female rats, if the drug is not protected by an enteric coating. The intra-duodenal bioavailability is approximately 70% and the oral bioavailability is approximately 15% in the dog.

Distribution: After absorption, omeprazole is rapidly distributed to extravascular sites, and about 95% is bound to plasma proteins. The distribution of ^{14}C-labelled omeprazole in the mouse was investigated by autoradiography. Radioactivity was initially found in the blood and most organs. Sixteen hours after administration, the drug was confined predominantly to the stomach wall. At 48 hours, the radioactivity was eliminated.

Penetration of omeprazole and/or its metabolites across the blood-brain and placental barriers was low.

Metabolism and Elimination: Omeprazole was extensively metabolized in all species studied. In rats and dogs approximately 20-30% of the dose was excreted as urinary metabolites and the remainder by biliary excretion as metabolites in the feces. Elimination was virtually complete within 72 hours. Identifiable metabolites constituted about 50% (rat) and 70% (dog) of the total metabolite excretion in 24 hours, and about 12% of the given dose in both species.

A study in lactating rats showed that omeprazole is excreted in breast milk. The concentration in the milk at 3-5 hours post dose was 100-200 times lower than the plasma concentration. It is not known if omeprazole is excreted in human milk.

Reproductive and Developmental Toxicology

In studies with male and female rats given oral doses of up to 138 mg/kg/day (approximately 500 times the recommended human dose), fertility and reproductive performance were not affected.

In rabbits, increased embryo-lethality and fetal resorption were observed at maternotoxic doses of 69 and 138 mg/kg/day (250 and 500 times the human dose). No maternal or fetal toxicity was observed in pregnant rats treated at doses ranging from 13.8 to 138 mg/kg/day (50 to 500 times the human dose). In rats, a slight decrease in litter size at birth and slightly impaired postnatal viability and growth were observed in offspring resulting from parents treated with high doses of 138 mg/kg/day (500 times the human dose) of omeprazole. Similar effects were not seen at lower doses.

Special Toxicology

Gastric ECL-Cell Carcinoids: Extensive investigations have been carried out to explain the ECL-cell hyperplasia and the gastric carcinoid findings in rats. Gastrin produced by the G-cells in the antrum plays an important role in the feedback control of gastric acid secretion.

In one series of experiments, the antrum of rats was surgically excluded from the rest of the stomach. The removal of acid from the antrum in this way led to pronounced hypergastrinemia and, secondary to this, gastric ECL-cell proliferation. Antrectomy, which removes the source of gastrin, led to a decrease in gastric ECL-cell density. These experiments indicated that gastrin has a direct trophic effect on gastric ECL-cells. In another series of experiments, high doses of omeprazole and a histamine H_2- receptor blocker caused hypergastrinemia and increased ECL-cell density. In antrectomized rats given a high dose of omeprazole, plasma gastrin levels remained normal, and consequently there was no increase in ECL-cell density. It has therefore been concluded that (i) inhibition of gastric acid secretion by large doses of omeprazole or a histamine H_2-receptor blocker evokes a natural feedback response leading to hypergastrinemia, (ii) long-standing hypergastrinemia leads to gastric ECL-cell proliferation, and (iii)

there is no direct trophic effect of omeprazole on gastric ECL-cells.

An additional long-term (24 months) toxicity study in female rats (1.8-14 mg/kg/day) confirmed that the ECL-cell carcinoids were extreme end-life tumors and that there was a linear correlation between carcinoid incidence and dose of omeprazole (1.8-140 mg/kg/day). In rats given omeprazole 14 mg/kg/day for 12 months, no carcinoids were found, and the ECL-cell hyperplasia recovered to normal during the next 12 months of no treatment.

No carcinoids have been found in mice, and in dogs following administration of 28 mg/kg/day for 7 years.

Investigation in man has demonstrated an initial moderate increase in gastrin levels during treatment with omeprazole, but no further increase occurred during long-term (up to 3 years) treatment. No significant changes have been found in the endocrine cells of the oxyntic gastric mucosa during short- or long-term treatment with omeprazole in man, to date. Chronic treatment of patients with Zollinger-Ellison syndrome with mean daily doses of omeprazole of 60 mg/day for up to 5 years has not influenced the pre-treatment hypergastrinemia, and no changes in the endocrine cells of the gastric mucosa have been found on repeat biopsies.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrLOSEC® Tablets, 20 mg Omeprazole (as Omeprazole Magnesium), submission control 257614, Product Monograph, CHEPLAPHARM Arzneimittel GmbH. (May 18, 2022)
2. PrLOSEC MUPS® Tablets, 10 mg and 20 mg Omeprazole (as Omeprazole Magnesium), submission control 275395, Product Monograph, CHEPLAPHARM Arzneimittel GmbH. (October 17, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] RIVA-OMEPRAZOLE DR

Omeprazole Magnesium Delayed Release Tablets

Read this carefully before you start taking **RIVA-OMEPRAZOLE DR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RIVA-OMEPRAZOLE DR**.

What is RIVA-OMEPRAZOLE DR used for?

RIVA-OMEPRAZOLE DR is used to treat problems caused by too much acid in the stomach such as:

- stomach ulcers (sores).
- duodenal ulcers (sores on the first part of the intestine).
- stomach and duodenal ulcers caused by a bacterium, *Helicobacter pylori*.
- reflux esophagitis (tissue damage caused by stomach acid and juices moving up the food tube).
- symptoms of reflux disease (e.g. heartburn, backup of stomach contents to the throat).
- ulcers caused by nonsteroidal anti-inflammatory drugs (drugs for pain and sore joints).
- dyspepsia, a group of symptoms which may include stomach pain / discomfort, heartburn and backup of stomach contents to the throat. Dyspepsia can be caused by the other conditions in this list.
- a rare condition where the stomach produces too much acid (Zollinger-Ellison syndrome).

How does RIVA-OMEPRAZOLE DR work?

RIVA-OMEPRAZOLE DR is a medicine called a proton pump inhibitor (PPI). RIVA-OMEPRAZOLE DR works by reducing the amount of acid made in your stomach.

What are the ingredients in RIVA-OMEPRAZOLE DR?

Medicinal ingredients: omeprazole magnesium

Non-medicinal ingredients: mannitol, microcrystalline cellulose, sodium starch glycolate, hydroxypropyl methylcellulose, talc, sodium stearyl fumarate, methacrylic acid copolymer, polyethylene glycol, titanium dioxide, iron oxide (red & yellow),

The imprinting ink consists of: shellac, isopropyl alcohol, iron oxide black, N-butyl alcohol, propylene glycol and ammonium hydroxide.

RIVA-OMEPRAZOLE DR comes in the following dosage forms:

Tablets of omeprazole 20 mg.

Do not use RIVA-OMEPRAZOLE DR if:

- you are allergic to omeprazole, substituted benzimidazoles or any of the other ingredients in RIVA-OMEPRAZOLE DR (see "What are the ingredients in RIVA-OMEPRAZOLE DR?").
- you are taking rilpivirine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RIVA-OMEPRAZOLE DR. Talk about any health conditions or problems you may have, including if you:

- have had any health problems in the past.
- have severe liver problems now or have had in the past.
- are pregnant or plan to become pregnant.
- are breastfeeding or planning to breastfeed, as omeprazole is excreted in breast milk.
- take any other medications, including ones you can buy without a prescription.
- are due to have a specific blood test (Chromogranin A).

Other warnings you should know about:

RIVA-OMEPRAZOLE DR is not recommended for use in patients under 18 years of age.

This medicine should be used at the lowest dose and for the shortest time suitable for your condition. Talk to your doctor if you have any concerns about your treatment.

Treatment in combination with antibiotics: if you experience symptoms such as severe (bloody or repeated watery) diarrhea, with or without fever, abdominal pain or tenderness, you may have bowel inflammation caused by a bacterial infection (*Clostridium difficile*). If this happens, stop taking the drug combination and call your healthcare professional immediately.

Tell your doctor or pharmacist about symptoms that may be a sign of a more serious problem in your stomach or intestine such as:

- trouble swallowing.
- unplanned weight loss.
- vomiting blood or food.
- black (blood-stained) stools.

Long-term use of PPIs may interfere with the absorption of Vitamin B12 from the diet. This may cause a shortage of Vitamin B12 in your body. Talk to your doctor about this risk.

Long-term use of PPIs may lead to low blood magnesium in some people. When blood magnesium is lower than normal, it may also lead to low blood calcium and low blood potassium.

Using PPIs for a long time (every day for a year or longer) may increase risks of broken bones of the hip, wrist or spine. Talk to your doctor about this risk.

Using RIVA-OMEPRAZOLE DR for a long period of time may cause a growth in your stomach (polyp), especially after one year.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
• Do not take RIVA-OMEPRAZOLE DR if you are taking rilpivirine (a drug used for HIV).

The following may interact with RIVA-Omeprazole:

- medication for HIV: RIVA-OMEPRAZOLE DR may decrease the effectiveness of some drugs used for HIV treatment; atazanavir, nelfinavir and saquinavir should not be used with RIVA-OMEPRAZOLE DR.
- a high-dose of methotrexate (a drug used in high doses to treat cancer). RIVA-OMEPRAZOLE DR may need to be temporarily withdrawn.
- clopidogrel, which is used for the prevention of blood clots. RIVA-OMEPRAZOLE DR may interact with this drug, therefore, use with clopidogrel should be avoided.
- drug effects may be influenced if RIVA-OMEPRAZOLE DR is taken at the same time as some drugs used to prevent fungal infections (itraconazole, ketoconazole, voriconazole), anxiety (diazepam), epilepsy (phenytoin), blood clotting (warfarin or other vitamin K blockers), transplant rejection (tacrolimus), poor circulation in the legs (cilostazol)*, heart problems (digoxin), treatment for tuberculosis (rifampin), St John's Wort (Hypericum perforatum) or a certain type of anticancer drug (erlotinib or any other anticancer drug from the same class).

  * not marketed in Canada

How to take RIVA-OMEPRAZOLE DR:

Follow your doctor's directions carefully. They may be different from the information contained in this leaflet.

- Take all doses of RIVA-OMEPRAZOLE DR that your doctor prescribes, even when you feel well. Doses every day are needed to help damaged areas heal.
- If you take RIVA-OMEPRAZOLE DR with antibiotic drugs, it is important that you take all medications at the right time of day for the whole treatment period. Studies have shown that patients who take their medications as prescribed have better ulcer healing rates and greater success getting rid of their H. pylori infection.
- Take RIVA-OMEPRAZOLE DR until your doctor tells you to stop. Even if you start to feel better in a few days, your symptoms may return if RIVA-OMEPRAZOLE DR is stopped too soon. RIVA-OMEPRAZOLE DR needs to be taken for the full treatment to help correct acid problems.
- RIVA-OMEPRAZOLE DR may be taken with food or on an empty stomach.
- Do not chew or crush your RIVA-OMEPRAZOLE DR. Swallow the RIVA-OMEPRAZOLE DR whole with half a glass of water.

Usual dose:

Your doctor may tell you to take RIVA-OMEPRAZOLE DR:

- 10*-40 mg once a day for 2-8 weeks to heal damaged areas.
- 10*-40 mg to control symptoms of reflux disease or to stop reflux esophagitis from coming back.
- 20 mg to stop ulcers from returning while you take your medicine for pain and joint problems.
- 60 mg once a day to treat Zollinger-Ellison syndrome
- In combination with antibiotic drugs for one week to treat ulcers caused by *Helicobacter pylori*.
  - as Omeprazole, Amoxicillin and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is RIVA-OMEPRAZOLE DR 20 mg, amoxicillin 1,000 mg and clarithromycin 500 mg, all twice daily for seven days.

- or as Omeprazole, Metronidazole and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is RIVA-OMEPRAZOLE DR 20 mg, metronidazole 500 mg and clarithromycin 250 mg, all twice daily for seven days.
- If your ulcer is bothering you, your doctor may recommend further treatment with RIVA-OMEPRAZOLE DR to make sure that your ulcer is healed.

*RIVA-OMEPRAZOLE DR is NOT available in 10 mg strength

Overdose:

If you think you, or a person you are caring for, have taken too much RIVA-OMEPRAZOLE DR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of RIVA-OMEPRAZOLE DR and remember within 12 hours, take it as soon as possible. Then go back to your regular schedule. However, if more than 12 hours have passed when you remember, do not take the missed tablet. Do not double the dose. Just take your next dose on time.

What are possible side effects from using RIVA-OMEPRAZOLE DR?

Like all medicines, RIVA-OMEPRAZOLE DR may cause side effects in some people. Side effects are usually mild and go away a short time after starting RIVA-OMEPRAZOLE DR.

These are not all the possible side effects you may have when taking RIVA-OMEPRAZOLE DR. If you experience any side effects not listed here, tell your healthcare professional.

Tell your doctor right away if you have any of these symptoms:

- New or worsening joint pain.
- Rash on your cheeks or arms that gets worse in the sun. Common side effects that may occur (≥ 1 in 100 patients):
- Headache.
- Diarrhea.
- Constipation.
- Abdominal pain.
- Nausea/ vomiting.
- Excess gas in stomach (flatulence).

Uncommon side effects that may occur (≥ 1 in 1,000 patients, but less than 1 in 100 patients):

- Dizziness.
- Feeling like you or your surroundings are moving (vertigo).
- Difficulty sleeping.
- Feeling sleepy.
- Sensation of burning / prickling / numbness.

Rare side effects that may occur (less than 1 in 1,000 patients):

- Dry mouth.
- Hair loss.
- Increased sweating.
- Taste disorders.

Stopping your PPI therapy after taking it for a long time may cause your symptoms to get worse and your stomach may increase acid production. Carefully follow your doctor's instructions when stopping RIVA-OMEPRAZOLE DR.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Skin reactions (such as skin rash, dermatitis, itchy skin and / or hives)		✓	
RARE			
Inflammation in the mouth		✓	
Gastrointestinal fungal infection		✓	
Inflammation of the kidney		✓	
Liver problems, i.e., inflammation of the liver with or without jaundice, impaired liver function			✓
Blood disorders (reduced number of cells in the blood, low blood sodium)		✓	
Sore joints and muscles		✓	
Muscular weakness		✓	
Development of breasts in males		✓	
Sensitivity to sunlight		✓	
Severe skin reactions			✓
Hypersensitive (allergic) reactions (such as swelling of tissues, fever, discomfort / tightness in chest and anaphylactic shock)			✓
Blurred vision		✓	
If you already have severe liver disease, you may experience disorientation / aggression / confusion / decreased consciousness		✓	
If you are very ill, you may feel confused, nervous, depressed or hallucinate		✓	
VERY RARE			
Low blood magnesium[θ] (which may result in low blood calcium and / or low blood potassium)		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Microscopic colitis (inflammation of the gut) • Chronic watery diarrhea • Abdominal pain, cramps or bloating • Weight loss • Nausea • Uncontrolled bowel movement • Signs of dehydration such as extreme thirst, less frequent urination, dark-coloured urine, fatigue, dizziness, confusion The symptoms of microscopic colitis can come and go frequently. If you have watery diarrhea that lasts more than a few days, contact your doctor.	✓		
Acute generalized exanthematous pustulosis (AGEP) (severe skin rash): small bumps surrounded by red skin, itching, fever, skin pain			✓
Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect more than one or more organs): fever, severe rash, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feel thirsty, urinate less often			✓

[θ] These would only be seen if a blood test was taken.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep all RIVA-OMEPRAZOLE DR in the original container until it is time for a dose. If you do not, moisture from the air may damage the RIVA-OMEPRAZOLE DR.

Store at room temperature (15-30 °C). Do not keep RIVA-OMEPRAZOLE DR in the bathroom medicine cabinet or other warm, moist places.

Do not use RIVA-OMEPRAZOLE DR after the expiry date marked on the pack.

Keep out of reach and sight of children.

If you want more information about RIVA-OMEPRAZOLE DR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.labriva.com , or by calling 1-800-363-7988

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