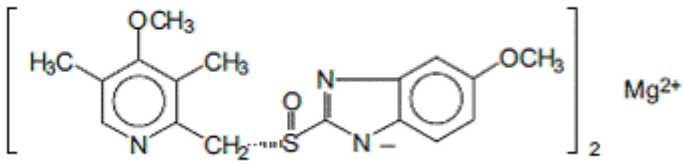
PRODUCT INFORMATION
MEPREZE® 20 mg ENTERIC COATED TABLETS

NAME OF THE MEDICINE

Esomeprazole is a proton pump inhibitor. The active ingredient in MEPREZE is esomeprazole magnesium, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable in vivo, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[(4- methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt.

The chemical structure of esomeprazole magnesium is:



CAS number: 161973-10-0
Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg$
Molecular weight: 713.12

DESCRIPTION

Esomeprazole magnesium is an off-white to slight coloured powder, soluble in N,N-Dimethyl formamide.

MEPREZE 20 mg tablets are comprised of enteric coated pellets containing esomeprazole magnesium as the active ingredient as well as the following inactive (excipient) ingredients:
Non-pareil seeds 40-50 (ARTG 108808), hyprolose, crospovidone, sucrose and maize starch, magnesium oxide light, purified talc, macrogol 6000, methacrylic acid - ethyl acrylate copolymer (1:1), glyceryl monostearate, macrogol 400, polysorbate 80, hypromellose phthalate, acetone, microcrystalline cellulose, iron oxide red, povidone, pregelatinised maize starch, silicon dioxide, lactose monohydrate and OPADRY complete film coating system 03B84893 PINK (ARTG 108603).

PHARMACOLOGY

Esomeprazole magnesium reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly

acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+, K^+-ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion
After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1. % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 2.

Table 2. Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Other effects related to acid inhibition
During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion. An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole. During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption
Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets. The enteric coating film, protecting the esomeprazole magnesium, dissolves at a pH above 5.5. Hence esomeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 50% after a single dose of 20 mg and increases to 68% after repeated once-daily administration.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution
The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose- dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion
The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

INDICATIONS

MEPREZE is indicated for the symptomatic relief of frequent heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs).

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Patients should be referred to their doctor for review if:

- They have significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena; and when gastric ulcer is suspected or present, as treatment with esomeprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- They are being treated for gastro-oesophageal reflux (heartburn) or gastro-oesophageal reflux disease (GORD) and symptoms persist for more than 14 days.
- Their symptoms persist or recur within two weeks of completing a course of esomeprazole.
- They have any other significant medical conditions.
- They are an adolescent or child under the age of 18 years.

Effects of acid inhibition
Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Concomitant therapy with 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 esomeprazole (40 mg p.o. daily) resulting in decreased exposure *to* the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES)-**

Acute interstitial nephritis
Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPis) including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency
Daily treatment with acid-suppressing medicines over a long period of time (e_g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria_

Osteoporotic fractures
Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

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 developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Special patient populations

CYP2C19 enzyme
Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

In case of clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased (see Interactions with other medicines).

Elderly
The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Gender
Following a single dose of 40 mg esomeprazole the mean area under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of esomeprazole.

Hepatic insufficiency
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration- time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment
No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats.

In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under in vivo conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. Esomeprazole should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 μmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore esomeprazole should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Results from studies in healthy subjects have shown a pharmacokinetic/pharrnacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p_o_ daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%_ Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

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 similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups_20

There are both observational and clinical studies on the clinical implications of a PKIPD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that affect esomeprazole

Clarithromycin
Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride
In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine
Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

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 similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Diazepam
Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs
Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin
Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is

recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin
Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus
Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

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

Antiretroviral drugs
Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption
The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Esomeprazole is an enantiomer of omeprazole. Co-administration of omeprazole and mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients

receiving proton pump inhibitors and mycophenolate mofetil. Use esomeprazole with caution in transplant patients receiving mycophenolate mofetil.

Potential interactions that have been excluded

Amoxycillin or quinidine
Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

Esomeprazole is well tolerated.

Clinical trials and post-marketing data
The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic system disorders
Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders
Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders
Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.
Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders
Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders
Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances
Rare: blurred vision

Ear and labyrinth disorders
Uncommon: vertigo

Respiratory, thoracic mediastinal disorders
Rare: bronchospasm

Gastrointestinal
Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: microscopic colitis

Hepatobiliary disorders
Uncommon: increased liver enzymes
Rare: hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders
Uncommon: dermatitis, pruritus, urticaria, rash
Rare: alopecia, photosensitivity
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Not known: subacute cutaneous lupus erythematosus (SCLE)

Muskuloskeletal, connective tissue and bone disorders
Rare: arthralgia, myalgia
Very rare: muscular weakness

Renal and urinary disorders
Very rare: interstitial nephritis

Reproductive system and breast disorders
Very rare: gynaecomastia

General disorders and administration site conditions
Rare: malaise, hyperhidrosis

DOSAGE AND ADMINISTRATION

MEPREZE tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic gastro-oesophageal reflux disease (GORD)

Adults
The recommended dose for the relief of heartburn and other symptoms of GORD is one MEPREZE 20 mg tablet once daily for at least 7 days, and up to 14 days. Patients should be referred to their doctor if symptoms persist or worsen while taking this course, or if symptoms persist or recur within two weeks of completing the course. Further investigation is recommended. Use for longer than 14 days should only be on medical advice.

Children and adolescents less than 18 years
Not recommended for use in children and adolescents below 18 years of age.

Geriatrics
Dose adjustment is not required in the elderly.

Hepatic insufficiency
Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg esomeprazole should not be exceeded (see PRECAUTIONS).

Renal insufficiency
Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

Contact the Poisons Information Centre on telephone 13 11 26 for advice on overdose management.

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

PRESENTATION AND STORAGE CONDITIONS

MEPREZE 20 mg enteric coated tablets - Light pink, oblong, biconvex, film coated tablets debossed with '20' on one side and 'CE' on the other side. Each tablet contains 20 mg esomeprazole (as esomeprazole magnesium) as enteric-coated pellets.

Available in Al/Al blister packs of 7 and 14 tablets.

Store below 25°C.

NAME AND ADDRESS OF SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road,
Macquarie Park NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

S3 (Pharmacist Only Medicine) – 14's pack

S2 (Pharmacy medicine) – 7's pack

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 04/08/2015

DATE OF MOST RECENT AMENDMENT: 21/06/2017