1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1.Name of the Medicinal Product

1.1 Product Name

- **Generic Name:**
  OMEPRAZOLE BP CAPSULES 20 mg
- **Brand Name:** OMYSIN
  OMISYN CAPSULES

1.2 Strength :
2 OMEPRAZOLE BP 20 mg

2.1 Pharmaceutical form:
Oral Capsule

2. Qualitative and quantitative composition:

Each capsule contains: Omeprazole BP 20 mg as enteric coated granules

3. Pharmaceutical Form:

- **Dosage Form:** Oral capsule
- **Visual & physical characteristics of the product:**

Pink capsule and clear transparent body, size '2' capsules filled with white to off white pellets

4. Clinical Particulars:

4.1 Therapeutic Indications:

Omeprazole is indicated in:

Adults:

• Treatment of duodenal ulcer, including prevention of relapse gastric ulcer and reflux oesophagitis.

• Long-term management of reflux oesophagitis and Zollinger-Ellison Syndrome.

• Symptomatic relief of heartburn in patients with gastro-oesophageal reflux disease (GORD) and the short-term relief of functional dyspepsia.

• Helicobacter pylori-positive duodenal ulcers as part of an eradication programme with appropriate antibiotics.

• Treatment of non-steroidal anti-inflammatory drugs (NSAID)-associated gastric and/or duodenal ulcer/erosions.

• Reduction of the risk to develop gastric and/or duodenal ulcer/erosions and reduction of the risk of relapse for previously healed gastric and/or duodenal ulcer/erosions in patients on NSAID treatment.

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

4.2 Posology and method of administration:

Condition for administration : Capsule should be swallowed whole with sufficient water and not to be opened *I* chewed or crushed

DOSAGE AND ADMINISTRATION

Omeprazole is recommended to be given in the morning and swallowed whole with a half glass of liquid. The capsules should not be chewed or crushed.

RECOMMENDED DOSAGES FOR ADULTS:

Duodenal ulcer:

20 mg once daily for two to four weeks.

In some duodenal ulcer patients refractory to other treatment regimens, 40 mg once daily may be effective.

Prevention of relapse in patients with duodenal ulcer:

10 mg once daily.

If necessary the dose can be increased to 20 –40 mg once daily.

The above recommended dosage regimens are inclusive of Helicobacter pylori-positive duodenal ulcers as part of the eradication programme with appropriate antibiotics.

Gastric ulcer and reflux oesophagitis:

20 mg once daily for four to eight weeks.

In some gastric ulcer and reflux oesophagitis patients refractory to other treatment regimens, 40 mg once daily may be effective.

For the long-term management of patients with reflux oesophagitis the recommended dose is 20 mg once daily. If necessary the dose can be increased to 20 –40 mg once daily.

In patients with severe or symptomatic recurrent reflux oesophagitis treatment can be continued with omeprazole at a dosage of 20 mg once daily.

NSAID-associated gastro-duodenal lesions with or without continued NSAID treatment:

20 mg once daily.

In most patients healing occurs within 4 weeks. For patients who may not be fully healed after the initial course healing usually occurs during a further 4 weeks of treatment.

Prevention of NSAID-associated gastro-duodenal lesions and dyspeptic symptoms:

20 mg once daily.

Symptomatic gastro-oesophageal reflux disease:

20 mg daily.

Patients may respond adequately to 10 mg daily, therefore individual dose adjustments should be considered.

If symptom control has not been achieved after 2 weeks of treatment with 20 mg daily further investigation is recommended.

Zollinger-Ellison Syndrome: 60 mg once daily.

The dosage should be adjusted individually and treatment continued as long as it is clinically indicated. With doses above 80 mg daily the dose should be divided and given twice daily.

There is very limited experience with the use of omeprazole in children (see WARNINGS).

Severe ulcerative reflux oesophagitis in children from one year and older:

Recommended dosages:

Weight	Dosage	
10 –20 kg:	10 mg once daily.	If needed increase to 20 mg once daily
>20 kg:	20 mg once daily.	If needed increase to 40 mg once daily

Elderly: Dose reductions are not necessary in elderly patients.

The long-term safety of omeprazole in patients with renal and hepatic impairment has not been established (see WARNINGS).

Impaired renal function: Dose reductions are not necessary in renal impairment.

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

4.3 Contraindication:

: Hypersensitivity to any of the ingredients. Safety in pregnancy and lactation has not been established.

4.4 Special Warnings and precautions for use:

1. WARNINGS: Symptomatic response to omeprazole therapy does not preclude the presence of gastric ulcer or malignancy or a malignant disease of the oesophagus. The administration of omeprazole in this situation may delay diagnosis (see Special Precautions).

2. Hepatic impairment may require a reduction in dose (see DOSAGE AND DIRECTIONS FOR USE).

3. There is very limited experience with the use of omeprazole in children.

4. The long-term safety of omeprazole in patients with renal and/or hepatic impairment has not been established.

5. This medicine may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

6. PREGNANCY AND LACTATION: Safety in pregnancy and lactation has not been established (see CONTRAINDICATIONS).

PRECAUTIONS: Effects related to acid inhibition: During long-term treatment gastric glandular cysts have been reported in increased frequency. These physiological changes result from pronounced inhibition of gastric acid secretion. Decreased gastric acidity increases gastric counts of bacteria normally present in the gastro-intestinal tract. Treatment with omeprazole may lead to an increased risk of gastro-intestinal infections such as Salmonella and Campylobacter.

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

4.5 Interaction with other medicinal products and other forms of interaction

Omeprazole is metabolised via the hepatic P450 cytochrome enzyme system, which may affect the metabolism of other medications metabolised by these enzymes, when given concomitantly. The elimination of diazepam, warfarin and phenytoin may be prolonged when omeprazole is given concomitantly.

Monitoring of INR and phenytoin serum levels is recommended and dosage reductions may be necessary when omeprazole is given concomitantly. There is a possible interaction of omeprazole with digoxin and a 10% increase in digoxin bioavailability may be expected.

There may be interactions with other medicines, which are also metabolised via the cytochrome P450 enzyme system.

4.6 Fertility, pregnancy and lactation

Pregnancy

Teratogenic Effects

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with Omeprazole in pregnant women. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester Omeprazole use.

Teratogenicity was not observed in animal reproduction studies with administration of oral esOmeprazole magnesium in rats and rabbits with doses about 68 times and 42 times, respectively, an oral human dose of 40 mg (based on a body surface area basis for a 60 kg person). However, changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 34 times an oral human dose of 40 mg *(see Animal Data).* Because of the observed effect at high doses of esOmeprazole magnesium on developing bone in rat studies, Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data: Four published epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used Omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls.

A population-based retrospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, from 1995 to 99, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used Omeprazole during pregnancy. The number of infants exposed *in utero* to Omeprazole that had any malformation, low birth weight, low Apgar score, or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the Omeprazole-exposed infants than the expected number in this population.

A population-based retrospective cohort study covering all live births in Denmark from 1996 to 2009, reported on 1,800 live births whose mothers used Omeprazole during the first trimester of pregnancy and 837, 317 live births whose mothers did not use any proton pump inhibitor. The overall rate of birth defects in infants born to mothers with first trimester exposure to Omeprazole was 2.9% and 2.6% in infants born to mothers not exposed to any proton pump inhibitor during the first trimester.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or Omeprazole in the first trimester (134 exposed to Omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to Omeprazole, an H2-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

A small prospective observational cohort study followed 113 women exposed to Omeprazole during pregnancy (89% first trimester exposures). The reported rate of major congenital malformations was 4% in the Omeprazole group, 2% in controls exposed to non-teratogens, and 2.8% in disease-paired controls. Rates of spontaneous and

elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight were similar among the groups.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous Omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Animal Data

Reproductive studies conducted with Omeprazole in rats at oral doses up to 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) did not disclose any evidence for a teratogenic potential of Omeprazole. In rabbits, Omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 3.4 to 34 times an oral human dose of 40 mg on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with Omeprazole at 13.8 to 138 mg/kg/day (about 3.4 to 34 times an oral human doses of 40 mg on a body surface area basis).

Nursing Mothers

Omeprazole is present in human milk. Omeprazole concentrations were measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of Omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of Omeprazole in 200 mL of milk. Caution should be exercised when Omeprazole are administered to a nursing woman.

Pediatric Use

Use of Omeprazole in pediatric and adolescent patients 2 to 16 years of age for the treatment of GERD and maintenance of healing of erosive esophagitis is supported by a) extrapolation of results from adequate and well-controlled studies that supported the approval of Omeprazole for adults, and b) safety and pharmacokinetic studies performed in pediatric and adolescent patients *[see Clinical Pharmacology, Pharmacokinetics, Pediatric* for pharmacokinetic information *(12.3)* and *Dosage and Administration (2)*, *Adverse Reactions (6.1)* and *Clinical Studies (14.6)]*. The safety and effectiveness of Omeprazole for the treatment of GERD in patients <1 year of age have not been established. The safety and effectiveness of Omeprazole for other pediatric uses have not been established.

4.7 Undesirable effects

ADVERSE REACTIONS

Body As a Whole: Hypersensitivity reactions including anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis,urticaria, (see **also *Skin* below**); fever; pain; fatigue; malaise;

Cardiovascular: Chest pain or angina, tachycardia, bradycardia,palpitations, elevated blood pressure, peripheral edema

Endocrine: Gynecomastia

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, stomatitis, abdominal swelling, dry mouth, microscopic colitis. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastroduodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with Omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Liver disease including hepatic failure (some fatal), liver necrosis(some fatal), hepatic encephalopathy hepatocellular disease, cholestatic disease, mixed hepatitis, jaundice, and elevations of liver function tests [ALT, AST, GGT, alkaline phosphatase, and bilirubin]

Infections and Infestations: *Clostridium difficile* associated diarrhea

Metabolism and Nutritional disorders: Hypoglycemia, hypomagnesemia, with or without hypocalcemia and/or hypokalemia, hyponatremia, weight gain

Musculoskeletal: Muscle weakness, myalgia, muscle cramps, joint pain, leg pain, bone fracture

Nervous System/Psychiatric: Psychiatric and sleep disturbances including depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, apathy, somnolence, anxiety, and dream abnormalities; tremors, paresthesia; vertigo

Respiratory: Epistaxis, pharyngeal pain

Skin: Severe generalized skin reactions including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, and erythema multiforme; photosensitivity; urticaria; rash; skin inflammation; pruritus; petechiae;purpura; alopecia; dry skin; hyperhidrosis

Special Senses: Tinnitus, taste perversion

Ocular: Optic atrophy, anterior ischemic optic neuropathy, optic neuritis, dry eye syndrome, ocular irritation, blurred vision, double vision

Urogenital: Interstitial nephritis, hematuria, proteinuria, elevated serum creatinine, microscopic pyuria, urinary tract infection, glycosuria, urinary frequency, testicular pain

Hematologic: Agranulocytosis (some fatal), hemolytic anemia, pancytopenia, neutropenia, anemia, thrombocytopenia, leukopenia, leucocytosis

4.8 Overdose

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience [see **ADVERSE REACTIONS**]. Symptoms were transient, and no serious clinical outcome has been reported when PRILOSEC was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

5. Pharmacological Properties:

5.1 PharmacodynamicProperties:

Clinical data: Pharmacodynamics:

The action of omeprazole is mediated by inhibition of the H^+ - K^+ ATPase in the gastric parietal cells. This enzyme, which is translocated from the tubulovesicular system to the apical plasma membrane on stimulation of acid secretion, -is responsible for the electro neutral exchange of H^+ and K^+ ions during formation of HCI. Omeprazole is absorbed from the gastro-intestinal tract. It reaches the parietal cells from the blood and diffuses into the secretory canaliculi, where it gets protonated and trapped. The protonated agent rearranges itself to form a sulfenic acid and a sulfenamide. The sulfenamide interacts covalently with sulfhydryl groups at critical sites in the extra cellular (luminal) domain of the membrane spanning H^+ - K^+ ATPase. Full inhibition occurs with two molecules of inhibitor bound per molecule of enzyme. It results in permanent inhibition of enzyme activity. Maximum effect occurs within 2 hours of omeprazole administration. Fifty percent of the maximum inhibition remains for 24 hours and the inhibition persists for up to 72 hours with one daily dosing, a plateau is reached after 4 days, and after discontinuation gastric acid secretory activity gradually returns to normal over 3 - 5 days.

Secretion of acid resumes only after insertion of new molecules of H^+ - K^+ ATPase into the luminal membrane. Since omeprazole acts at the final stage in the formation of HCI, the drug inhibits acid secretion induced by all stimuli, including intracellular mediators such as cyclic AMP.

5.2 Pharmacokinetic Properties:

Clinical Data: Pharmacokinetics:

Omeprazole .is acid-labile and is formulated as enteric-coated granules. Absorption is rapid and begins after the granules leave the stomach. Orally administered omeprazole is absorbed rapidly but to a variable extent. Bioavailability of omeprazole depends on dose and gastric pH and may reach upto 70% with repeated administration. In the plasma, more than 95% of Omeprazole is protein bound to albumin and glycoprotein. Omeprazole is cleared from the circulation by hepatic metabolism with a half-life of 30 to 90 minutes. Omeprazole is almost completely metabolized in the liver and rapidly eliminated mostly in the urine. Although its elimination half-life from plasma is about 0.5 to 3 hours, it's duration of action on the gastric parietal cells is much longer. Omeprazole is extensively metabolized by the liver. The plasma elimination half-life is less than 2 hours, while the acid inhibitory effect lasts for more than 24 hours, apparently because of prolonged binding to the parietal H^+ - K^+ -ATPase enzyme. When the drug is discontinued, secretory activity returns over 3 - 5 days. About 20% of the administered dose of Omeprazole is excreted in the feces and remaining 80% in the urine.

Bioavailability of two single-dose oral formulations of omeprazole 20 mg: an open-label, randomized sequence, two-period crossover comparison in healthy Mexican adult volunteers.

Poo JL[1], Galán JF, Rosete A, de Lago A, Oliva I, González-de la Parra M, Jiménez P, Burke-Fraga V, Namur S.

Author information

Abstract

BACKGROUND:

Omeprazole is a proton-pump inhibitor that acts to reduce acid secretion in the stomach and is used for treating various acid-related gastrointestinal disorders. There are several generic formulations of omeprazole available in Mexico; however, a literature search failed to identify published data concerning the bioavailability of these formulations in the Mexican population.

OBJECTIVE:

The aim of this study was to compare the bioavailability of 2 oral formulations of omeprazole 20-mg capsules, marketed for use in Mexico, in healthy volunteers: Inhibitron (test formulation) and LosecA 20 mg (reference formulation).

METHODS:

This study used a single-dose, open-label, randomized sequence, 2 x 2 crossover (2 administration periods x 2 treatments) design to compare the 2 formulations. Eligible subjects were healthy adult Mexican volunteers of both sexes. Subjects were randomly assigned in a 1:1 ratio to receive a single 20-mg dose of the test formulation

followed by the reference formulation, or vice versa, with a 7-day washout period between administration periods. After a 12-hour (overnight) fast, subjects received a single, 20-mg dose of the corresponding formulation. Plasma samples were obtained over a 12-hour period after administration. Plasma omeprazole concentrations were analyzed by a nonstereospecific high-performance liquid chromatography method. For analysis of pharmacokinetic properties, including C(max), AUC from time 0 (baseline) to time t (AUC(0-t)), and AUC from baseline to infinity (AUC(0-infinity)), blood samples were drawn at baseline and 0.17, 0.33, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.50, 3, 4, 6, 8, and 12 hours after administration. The formulations were considered bioequivalent if the natural log (ln)-transformed ratios of C(max) and AUC were within the predetermined equivalence range of 80% to 125%, and if P <or= 0.05 for the 90% CIs. Tolerability was determined by clinical assessment, monitoring vital signs, laboratory analysis results, and subject interviews regarding adverse events (AEs). AEs were considered serious when the patient outcome was death, life threatening, required hospitalization, led to disability, or required intervention to prevent permanent impairment or damage.

RESULTS:

Thirty-four subjects were enrolled and completed the study (25 men and 9 women; mean [SD] age, 24.7 [5.5] years; weight, 64.3 [8.9] kg; and height, 167 [8] cm). Seventeen subjects received the test formulation first. No period or sequence effect was observed. The 90% CIs for the corresponding differences of ln C(max), ln AUC(0-t), and ln AUC(0-infinity) were 86.70% to 109.76%, 93.81% to 108.22%, and 102.09% to 114.21%, respectively (all, P<0.05), meeting the predetermined criteria for bioequivalence. Eight patients experienced 13 AEs that appeared to be not associated with study drug administration; none of the AEs were considered serious.

CONCLUSIONS:

In this small study in healthy Mexican adult volunteers, a single, 20-mg dose of the test formulation appeared to be bioequivalent to the reference formulation, based on the rate and extent of absorption. Both formulations were generally well tolerated.

6 Pharmaceutical Particulars:

6.1 Incompatibilities:

Not Applicable

6.2 Shelf Life:

24 months

6.3 Special Precautions for storage:

Store below 30°C.

6.4 Nature of contents of container:

Alu Foil Blister

6.5 Special requirements for disposal:

No special requirements.

7 Registrant :

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7. Date of revision of the text:

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8. Dosimetry (if applicable):

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9. Instructions for Preparation of Radiopharmaceuticals: (Not Applicable)