

1.14.2.3 Final labeling text

Final package leaflet in [MS-Word format](#) and [Pdf format](#) of Accord Healthcare, Inc are provided in this section.

[Structured product labeling](#) for Esomeprazole Sodium for Injection, 40 mg/vial is enclosed in this section.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Esomeprazole sodium for Injection safely and effectively. See full prescribing information for Esomeprazole sodium for Injection.

ESOMEPRAZOLE sodium for Injection, for intravenous use
Initial US Approval: 2005

-----**RECENT MAJOR CHANGES**-----

Warnings and Precautions, Interactions with Diagnostic Investigations for Neuroendocrine Tumors (5.9)	03/2014
Contraindications (4)	12/2014
Warnings and Precautions, Acute Interstitial Nephritis (5.3)	12/2014

-----**INDICATIONS AND USAGE**-----

Esomeprazole sodium for Injection is a proton pump inhibitor indicated for the treatment of:

- Gastroesophageal Reflux Disease (GERD) with erosive esophagitis (EE) in adults and pediatric patients greater than one month of age, when oral therapy is not possible or appropriate. (1.1)

-----**DOSAGE AND ADMINISTRATION**-----

GERD – with Erosive Esophagitis. (2.1):

- Adults: Dose is either 20 mg or 40 mg esomeprazole given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 minutes to 30 minutes).
- Pediatric: Give the following doses once daily as an intravenous infusion over 10 minutes to 30 minutes. (2.1):
 - 1 year to 17 years:
 - o Body weight less than 55 kg: 10 mg
 - o Body weight 55 kg or greater: 20 mg
 - 1 month to less than 1 year of age: 0.5 mg/kg
- For patients with severe liver impairment (Child Pugh Class C), a maximum dose of 20 mg once daily of esomeprazole should not be exceeded. (2.1, 8.6, 12.3)

-----**DOSAGE FORMS AND STRENGTHS**-----

Esomeprazole sodium for Injection is supplied as a freeze-dried powder containing 40 mg of esomeprazole per single-use vial. (3)

-----**CONTRAINDICATIONS**-----

Patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles (angioedema and anaphylaxis have occurred). (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Symptomatic response to therapy with esomeprazole does not preclude the presence of gastric malignancy. (5.1)
- Atrophic gastritis has been noted with long-term omeprazole therapy. (5.2)
- Acute interstitial nephritis has been observed in patients taking PPIs. (5.3)

- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea. (5.4)
- Avoid concomitant use of esomeprazole with clopidogrel. (5.5)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.6)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs. (5.7)
- Avoid concomitant use of esomeprazole with St. John’s Wort or rifampin due to the potential reduction in esomeprazole levels. (5.8, 7.2)
- Interactions with diagnostic investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors. (5.9, 12.2)

-----**ADVERSE REACTIONS**-----

Most common adverse reactions (≥1%) are headache, flatulence, nausea, abdominal pain, injection site reaction, diarrhea, dry mouth, dizziness/vertigo, constipation and pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Accord Healthcare Inc. at 1-866-941-7875 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- Esomeprazole may interfere with drugs for which gastric pH affects bioavailability (e.g. ketoconazole, iron salts, erlotinib, digoxin and mycophenolate mofetil). Patients treated with esomeprazole and digoxin may need to be monitored for digoxin toxicity. (7)
- Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. (7)
- Esomeprazole may reduce the plasma levels of atazanavir, nelfinavir, and saquinavir. (7)
- Concomitant treatment with a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. (7)
- May increase systemic exposure of cilostazol and an active metabolite. Consider dose reduction. (7)
- Clopidogrel: Esomeprazole decreases exposure to the active metabolite of clopidogrel. (7)
- Tacrolimus: Esomeprazole may increase serum levels of tacrolimus (7.2)
- Methotrexate: Esomeprazole may increase serum levels of methotrexate. (7.3)

-----**USE IN SPECIFIC POPULATIONS**-----

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Treatment of Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis

Esomeprazole sodium for Injection is indicated for the short-term treatment of GERD with erosive esophagitis in adults and pediatric patients 1 month to 17 years, inclusively as an alternative to oral therapy when oral esomeprazole is not possible or appropriate.

2 DOSAGE AND ADMINISTRATION

General Information

Esomeprazole sodium for Injection should not be administered concomitantly with any other medications through the same intravenous site and/or tubing. The intravenous line should always be flushed with either 0.9% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP or 5% Dextrose Injection, USP both prior to and after administration of Esomeprazole sodium for Injection.

The admixture should be stored at room temperature up to 30°C (86°F) and should be administered within the designated time period as listed in Table 1 below. No refrigeration is required.

Table 1 Storage Time for Final (diluted) Product

Diluent	Administer within:
0.9% Sodium Chloride Injection, USP	12 hours
Lactated Ringer's Injection, USP	12 hours
5% Dextrose Injection, USP	6 hours

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

As soon as oral therapy is possible or appropriate, intravenous therapy with Esomeprazole sodium for Injection should be discontinued and the therapy should be continued orally.

2.1 GERD with Erosive Esophagitis

Adult Patients

The recommended adult dose is either 20 mg or 40 mg esomeprazole given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 minutes to 30 minutes). Safety and efficacy of Esomeprazole sodium for Injection as a

treatment of GERD patients with erosive esophagitis for more than 10 days have not been demonstrated.

Dosage adjustment is not required in patients with mild to moderate liver impairment (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a maximum dose of 20 mg once daily of esomeprazole should not be exceeded [see *Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

Pediatric Patients

The recommended doses for children ages 1 month to 17 years, inclusive, are provided below. Dose should be infused over 10 minutes to 30 minutes.

1 year to 17 years:

Body weight less than 55 kg: 10 mg

Body weight 55 kg or greater: 20 mg

1 month to less than 1 year of age: 0.5 mg/kg

2.3 Preparation and Administration Instructions

General Information

The reconstituted solution of Esomeprazole sodium for Injection should be stored at room temperature up to 30°C (86°F) and administered within 12 hours after reconstitution. (Administer within 6 hours if 5% Dextrose Injection is used after reconstitution). No refrigeration is required [see *Dosage and Administration (2), Table I*].

Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis

Preparation Instructions for Adult Patients

Intravenous Injection (40 mg vial) over no less than 3 minutes

The freeze-dried powder should be reconstituted with 5 mL of 0.9% Sodium Chloride Injection, USP.

Withdraw 5 mL of the reconstituted solution and administer as an intravenous injection over no less than 3 minutes.

Preparation Instructions for Pediatric Patients

Intravenous Infusion (40 mg) over 10 minutes to 30 minutes

A solution for intravenous infusion is prepared by first reconstituting the contents of one vial* with 5 mL of 0.9%

Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP or 5% Dextrose Injection, USP and further diluting the resulting solution to a final volume of 50 mL. The resultant concentration after diluting to a final volume of 50 mL is 0.8 mg/mL (for 40 mg vial). The solution (admixture) should be administered as an intravenous infusion over a period of 10 minutes to 30 minutes.

*For patients 1 month to less than 1 year of age, first calculate the dose (0.5 mg/kg) to determine the vial size needed.

3 DOSAGE FORMS AND STRENGTHS

Esomeprazole sodium for Injection is supplied as a freeze-dried white to off-white powder containing 40 mg of esomeprazole per single-use vial.

4 CONTRAINDICATIONS

Esomeprazole sodium for Injection is contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria [*see Adverse Reactions (6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Concomitant Gastric Malignancy

Symptomatic response to therapy with esomeprazole does not preclude the presence of gastric malignancy.

5.2 Atrophic Gastritis

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer.

5.3 Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops [*see Contraindications (4)*].

5.4 *Clostridium difficile* associated diarrhea

Published observational studies suggest that PPI therapy like esomeprazole may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [*see Adverse Reactions (6.2)*].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

5.5 Interactions with Clopidogrel

Avoid concomitant use of esomeprazole with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using esomeprazole consider alternative anti-platelet therapy [see *Drug Interactions (7), Clinical Pharmacology (12.3)*].

5.6 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 *Dosage and Administration (2), Adverse Reactions (6.2)*].

5.7 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see *Adverse Reactions (6.2)*].

5.8 Concomitant use of esomeprazole with St. John's Wort or Rifampin

Drugs which induce CYP2C19 or CYP3A4 (such as St John's Wort or rifampin) can substantially decrease esomeprazole concentrations [see *Drug Interactions (7)*]. Avoid concomitant use of esomeprazole with St. John's Wort or rifampin.

5.9 Interactions with Investigations for Neuroendocrine

Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary [see *Clinical Pharmacology (12.2)*].

5.10 Concomitant use of esomeprazole with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients [see *Drug Interactions (7.3)*]

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience with Intravenous esomeprazole

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

The safety of intravenous esomeprazole is based on results from clinical trials conducted in three different populations including patients having symptomatic GERD with or without a history of erosive esophagitis (n=199), patients with erosive esophagitis (n=160), healthy subjects (n=204).

Symptomatic GERD and Erosive Esophagitis Trials

The data described below reflect exposure to esomeprazole in 359 patients. Esomeprazole was studied only in actively-controlled trials. The population was 18 to 77 years of age; 45% Male, 52% Caucasian, 17% Black, 3% Asian, 28% Other, and had either erosive reflux esophagitis (44%) or GERD (56%). Most patients received doses of either 20 or 40 mg either as an infusion or an injection. Adverse reactions occurring in $\geq 1\%$ of patients treated with intravenous esomeprazole (n=359) in clinical trials are listed below:

Table 2

**Adverse reactions occurring at an incidence
≥ 1% in the esomeprazole group**

Adverse Reactions	% of patients Esomeprazole Intravenous (n=359)
Headache	10.9
Flatulence	10.3
Nausea	6.4
Abdominal pain	5.8
Diarrhea	3.9
Mouth dry	3.9
Dizziness/vertigo	2.8
Constipation	2.5
Injection site reaction	1.7
Pruritus	1.1

Intravenous treatment with esomeprazole 20 and 40 mg administered as an injection or as an infusion was found to have a safety profile similar to that of oral administration of esomeprazole.

Pediatric

A randomized, open-label, multi-national study to evaluate the pharmacokinetics of repeated intravenous doses of once daily esomeprazole in pediatric patients 1 month to 17 years old, inclusive was performed. The safety results are consistent with the known safety profile of esomeprazole and no unexpected safety signals were identified [see *Clinical Pharmacology (12.3)*].

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of esomeprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing Reports - There have been spontaneous reports of adverse events with postmarketing use of esomeprazole. These reports occurred rarely and are listed below by body system:

Blood And Lymphatic System Disorders: agranulocytosis, pancytopenia; **Eye Disorders:** blurred vision; **Gastrointestinal Disorders:** pancreatitis; stomatitis; microscopic colitis; **Hepatobiliary Disorders:** hepatic failure, hepatitis with or without jaundice; **Immune System Disorders:** anaphylactic reaction/shock; **Infections and Infestations:** GI candidiasis; **Metabolism and**

nutritional disorders: hypomagnesemia with or without hypocalcemia and/or hypokalemia; **Musculoskeletal And Connective Tissue Disorders:** muscular weakness, myalgia, bone fracture; **Nervous System Disorders:** hepatic encephalopathy, taste disturbance; **Psychiatric Disorders:** aggression, agitation, depression, hallucination; **Renal and Urinary Disorders:** interstitial nephritis; **Reproductive System and Breast Disorders:** gynecomastia; **Respiratory, Thoracic and Mediastinal Disorders:** bronchospasm; **Skin and Subcutaneous Tissue Disorders:** alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN, some fatal).

Other adverse events not observed with esomeprazole, but occurring with omeprazole can be found in the omeprazole package insert, **ADVERSE REACTIONS** section.

7 DRUG INTERACTIONS

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

In vitro and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin. Post-marketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance.

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of esomeprazole 40 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid

concomitant administration of esomeprazole with clopidogrel. When using esomeprazole, consider use of alternative anti-platelet therapy [see *Clinical Pharmacology (12.3)*].

Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased C_{max} and AUC of cilostazol by 18% and 26%, respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydro-cilostazol, which has 4-7 times the activity of cilostazol, were increased by 29% and 69%, respectively. Co-administration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above mentioned active metabolite. Therefore, a dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered.

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. Dose adjustment of esomeprazole is not normally required for the recommended doses. However, in patients who may require higher doses, dose adjustment may be considered.

Drugs known to induce CYP2C19 or CYP3A4 (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's wort, an inducer of CYP3A4. In a cross-over study in 12 healthy male subjects, St John's wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolizers (C_{max} and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolizers (C_{max} and AUC decreased by 49.6% and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with esomeprazole.

Co-administration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole.

Concomitant use of atazanavir and proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these 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. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg daily), AUC was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75%, respectively, for nelfinavir and M8. Following multiple doses of atazanavir (400 mg daily) and omeprazole (40 mg daily, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported with an increase in AUC by 82%, in C_{max} by 75% and in C_{min} by 106% following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily co-administered days 11 to 15. Dose reduction of saquinavir should be considered from the safety perspective for individual patients. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant changes in the pharmacokinetic profiles of esomeprazole or these NSAIDs.

Due to its effects on gastric acid secretion, esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole.

Esomeprazole is an enantiomer of omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Co-administration of digoxin with esomeprazole is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with esomeprazole.

Co-administration of omeprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving esomeprazole and MMF. Use esomeprazole with caution

in transplant patients receiving MMF [*see Clinical Pharmacology (12.3)*].

7.1 Interactions with Investigations of Neuroendocrine Tumors

Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels which may interfere with investigations for neuroendocrine tumors [*see Warnings and Precautions (5.9), Clinical Pharmacology 12.2*].

7.2 Tacrolimus

Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.

7.3 Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) 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 Warnings and Precautions (5.10)*].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with esomeprazole in pregnant women. Esomeprazole is the s-isomer of omeprazole. 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, esomeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Esomeprazole is the S-isomer of omeprazole. Four 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 1995-99, 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 1996-2009, 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

Reproduction studies have been performed with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 41 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole magnesium.

A pre-and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg/kg/day (about 17 times an oral human dose of 40 mg on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses equal to or greater than 14 mg/kg/day (about 3.4 times an oral human dose of 40 mg on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

Effects on maternal bone were observed in pregnant and lactating rats in a pre-and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

A pre-and postnatal development study in rats with esomeprazole strontium (using equimolar doses compared to esomeprazole magnesium study) produced similar results in dams and pups as described above.

8.3 Nursing Mothers

Esomeprazole is likely present in human milk. Esomeprazole is the S-isomer of omeprazole and limited data indicate that maternal doses of omeprazole 20 mg daily produce low levels in human milk. Caution should be exercised when Esomeprazole sodium for Injection is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of Esomeprazole sodium for Injection have been established in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive Esophagitis [see *Clinical Pharmacology, Pharmacokinetics (12.3)*]. However, effectiveness has not been established in patients less than 1 month of age.

1 month to 17 years of age

Use of Esomeprazole sodium for Injection in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive Esophagitis is supported by: a) results observed from a pharmacokinetic (PK) study on Esomeprazole sodium for Injection performed in pediatric patients, b) predictions from a population PK model comparing I.V. PK data between adult and pediatric patients, and c) relationship between exposure and pharmacodynamic results obtained from adult I.V. and pediatric oral data and d) PK results already included in the current approved labeling and from adequate and well-controlled studies that supported the approval of Esomeprazole sodium for Injection for adults.

Neonates 0 to 1 month of age

Following administration of Esomeprazole sodium for Injection in neonates the geometric mean (range) for CL was 0.17 L/h/kg (0.04 L/h/kg- 0.32 L/h/kg).

The safety and effectiveness of Esomeprazole sodium for Injection in neonates have not been established.

Juvenile Animal Data

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about 34 to 68 times a daily human dose of 40 mg based on body surface area. Increases in death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight

gain, femur weight and femur length, and decreases in overall growth [see *Nonclinical Toxicology (13.2)*].

8.5 Geriatric Use

Of the total number of patients who received oral esomeprazole in clinical trials, 1,459 were 65 to 74 years of age and 354 patients were ≥ 75 years of age.

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

For adult patients with GERD, no dosage adjustment is necessary in patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). For patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded [see *Dosage and Administration (2)*, *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

The minimum lethal dose of esomeprazole sodium in rats after bolus administration was 310 mg/kg (about 75 times the human dose on a body surface area basis). The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia and intermittent clonic convulsions.

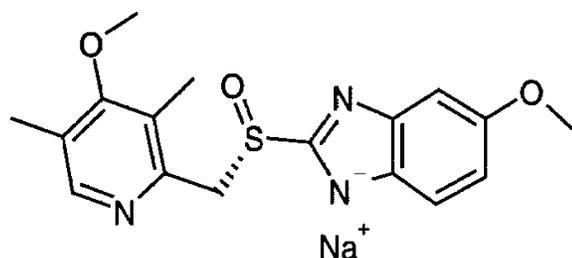
The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single oral doses of 80 mg and intravenous doses of 308 mg of esomeprazole over 24 hours were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert -ADVERSE REACTIONS). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current

information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

11 DESCRIPTION

The active ingredient in Esomeprazole sodium for Injection is (*S*)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1 *H*-benzimidazole sodium, a proton pump inhibitor that inhibits gastric acid secretion. Esomeprazole is the *S*-isomer of omeprazole, which is a mixture of the *S*- and *R*- isomers. Its empirical formula is $C_{17}H_{18}N_3O_3SNa$ with molecular weight of 367.4 g/mol (sodium salt) and 345.4 g/mol (parent compound). Esomeprazole sodium is very soluble in water and freely soluble in ethanol (95%). The structural formula is:



Esomeprazole sodium for Injection is supplied as a sterile, freeze-dried, white to off-white, porous cake or powder in a 6 mL vial, intended for intravenous administration after reconstitution with 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP or 5% Dextrose Injection, USP. Esomeprazole sodium for Injection contains esomeprazole sodium 42.5 mg equivalent to esomeprazole 40 mg, edetate disodium 1.5 mg and sodium hydroxide q.s. for pH adjustment. The pH of reconstituted solution of Esomeprazole sodium for Injection for Injection depends on the reconstitution volume and is in the pH range of 9 to 11. The stability of esomeprazole sodium in aqueous solution is strongly pH dependent. The rate of degradation increases with decreasing pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+ -ATPase in the gastric parietal cell. The *S*- and *R*-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the

final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

12.2 Pharmacodynamics

Antisecretory Activity

The effect of intravenous esomeprazole on intragastric pH was determined in two separate studies. In the first study, 20 mg of Esomeprazole sodium for Injection was administered intravenously once daily at constant rate over 30 minutes for 5 days. Twenty-two healthy subjects were included in the study. In the second study, 40 mg of Esomeprazole sodium for Injection was administered intravenously once daily at constant rate over 30 minutes for 5 days. Thirty-eight healthy subjects were included in the study.

Table 3

Effect of Esomeprazole sodium for Injection on Intragastric pH on Day 5

	Esomeprazole 20 mg (n=22)	Esomeprazole 40 mg (n=38)
% Time Gastric pH>4 (95% CI)	49.5 41.9-57.2	66.2 62.4-70.0

Gastric pH was measured over a 24-hour period

In a study in *H. pylori* negative healthy Caucasian volunteers (n =24), the % time over 24 hours (95 % CI) when intragastric pH was > 6 and > 7 was 52.3 % (40.3 – 64.4) and 4.8 % (1.8 – 7.8), respectively during administration of esomeprazole as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours.

In a study in *H. pylori* positive and *H. pylori* negative healthy Chinese subjects (overall n = 19), the % time over 24 hours (95 % CI) when intragastric pH was > 6 and > 7 was 53% (45.6 – 60.3) and 15.1 % (9.5 – 20.7) in the overall study population during administration of esomeprazole as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours. When comparing *H. pylori* positive (n =8) vs. negative (n =11) subjects, the percentage of time in a 24 h period with intragastric pH > 6 [59 % vs. 47 %] and with pH > 7 [17 % vs. 11 %] tended to be larger in the *H. pylori* positive subjects.

Serum Gastrin Effects

In oral studies, the effect of esomeprazole on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-

12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum Chromogranin A (CgA) levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

Enterochromaffin-like (ECL) Cell Effects

There are no data available on the effects of intravenous esomeprazole on ECL cells.

In 24-month carcinogenicity studies of oral omeprazole in rats, a dose-related significant occurrence of gastric ECL cell carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals [*see Nonclinical Toxicology, (13.1)*]. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H₂-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3,000 patients (both children and adults) treated orally with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients.

In over 1,000 patients treated with esomeprazole (10, 20 or 40 mg/day) up to 6-12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

Esomeprazole had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of esomeprazole on the endocrine system were assessed using omeprazole studies. Omeprazole given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

12.3 Pharmacokinetics

Absorption

The pharmacokinetic profile of esomeprazole 20 mg and 40 mg was determined in 24 healthy volunteers for the 20 mg dose and 38 healthy volunteers for the 40 mg dose following once daily administration of 20 mg and 40 mg of esomeprazole by constant rate over 30 minutes for five days. The results are shown in the following table:

Table 4

Pharmacokinetic Parameters of esomeprazole Following I.V. Dosing for 5 days

Parameter	Esomeprazole 20 mg	Esomeprazole 40 mg
AUC ($\mu\text{mol}\cdot\text{h/L}$)	5.11 (3.96:6.61)	16.21 (14.46:18.16)
C_{max} ($\mu\text{mol/L}$)	3.86 (3.16:4.72)	7.51 (6.93:8.13)
$t_{1/2}$ (h)	1.05 (0.90:1.22)	1.41 (1.30:1.52)

Values represent the geometric mean (95% CI)

During administration of esomeprazole over 24 hours as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours (for a total of 24 hours) in healthy volunteers ($n = 24$), esomeprazole PK parameters [geometric mean value (95 % CI)] were as follows: AUC_t 111.1 $\mu\text{mol}\cdot\text{h/L}$ (100.5-122.7 $\mu\text{mol}\cdot\text{h/L}$), C_{max} 15.0 $\mu\text{mol/L}$ (13.5-16.6 $\mu\text{mol/L}$), and steady state plasma concentration (C_{ss}) 3.9 $\mu\text{mol/L}$ (3.5-4.5 $\mu\text{mol/L}$).

In a Caucasian healthy volunteer study evaluating esomeprazole 80 mg over 30 minutes, followed by 8 mg/h over 23.5 h, systemic esomeprazole exposures were modestly higher (~ 17 %) in the CYP2C19 intermediate metabolizers (IM; $n = 6$) compared to extensive metabolizers (EM; $n = 17$) of CYP2C19. Similar PK differences were noted across these genotypes in a Chinese healthy volunteer study that included 7 EMs and 11 IMs. There is very limited PK information for poor metabolizers (PM) from these studies.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein

binding is constant over the concentration range of 2- 20 $\mu\text{mol/L}$. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion

Esomeprazole is excreted as metabolites primarily in urine but also in feces. Less than 1% of parent drug is excreted in the urine. Esomeprazole is completely eliminated from plasma, and there is no accumulation during once daily administration. The plasma elimination half-life of intravenous esomeprazole is approximately 1.1 to 1.4 hours and is prolonged with increasing dose of intravenous esomeprazole. During administration of esomeprazole over 24 hours as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours plasma clearance (CL) is approximately 5.9 to 7.2 L/h.

Concomitant Use with Clopidogrel

Results from a crossover study in healthy subjects have shown a pharmacokinetic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. once daily) when co-administered for 30 days. Exposure to the active metabolite of clopidogrel was reduced by 35% to 40% over this time period. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation was related to the change in the exposure to clopidogrel active metabolite.

Concomitant Use with Mycophenolate Mofetil

Administration of omeprazole 20 mg twice daily for 4 days and a single 1000 mg dose of MMF approximately one hour after the last

dose of omeprazole to 12 healthy subjects in a cross-over study resulted in a 52% reduction in the C_{max} and 23% reduction in the AUC of MPA.

Specific Populations

Investigation of age, gender, race, renal, and hepatic impairment and metabolizer status has been made previously with oral esomeprazole. The pharmacokinetics of esomeprazole is not expected to be affected differently by intrinsic or extrinsic factors after intravenous administration compared to oral administration. The same recommendations for dose adjustment in special populations are suggested for intravenous esomeprazole as for oral esomeprazole.

Geriatric

In oral studies, the AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Pediatric

In a randomized, open-label, multi-national, repeated dose study, esomeprazole PK was evaluated following a once-daily 3-minute injection in a total of 50 pediatric patients 0 to 17 years old, inclusive. Esomeprazole plasma AUC values for 20 mg esomeprazole were 183% and 60% higher in pediatric patients aged 6 – 11 years and 12 –17 years respectively compared to adults given 20 mg. Subsequent pharmacokinetic analyses predicted that a dosage regimen of 0.5 mg/kg once- daily for pediatric patients 1-11 months of age, 10 mg for pediatric patients 1-17 years with body weight ≤ 55 kg, and 20 mg for pediatric patients 1-17 years with body ≥ 55 kg would achieve comparable steady-state plasma exposures (AUC_{0-24}) to those observed in adult patients administered 20 mg of esomeprazole once every 24 hours. Further, increasing the infusion duration from 3 minutes to 10 minutes or 30 minutes was predicted to produce steady-state C_{max} values that were comparable to those observed in adult patients at the 40 mg and 20 mg esomeprazole doses.

Gender

In oral studies, the AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Similar differences have been seen for intravenous administration of esomeprazole. Dosage adjustment based on gender is not necessary.

Hepatic Impairment

In oral studies, the steady state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients

each with mild (Child Pugh Class A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a maximum dose of 20 mg once daily should not be exceeded [see *Dosage and Administration (2), Use in Specific Populations (8.6)*].

There are no pharmacokinetic data available for esomeprazole administered as continuous intravenous administration in patients with liver impairment. The pharmacokinetics of omeprazole 80 mg over 30 minutes, followed by 8 mg/h over 47.5 hours in patients with mild (Child Pugh Class A; n=5), moderate (Child Pugh Class B; n=4) and severe (Child Pugh Class C; n=3) liver impairment were compared to those obtained in 24 male and female healthy volunteers. In patients with mild and moderate liver impairment, omeprazole clearance and steady state plasma concentration was approximately 35% lower and 50% higher, respectively, than in healthy volunteers. In patients with severe liver impairment, the omeprazole clearance was 50% of that in healthy volunteers and the steady state plasma concentration was double that in healthy volunteers.

Renal Impairment

The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of esomeprazole is excreted unchanged in urine.

12.4 Microbiology

Effects on Gastrointestinal Microbial Ecology

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 hospitalized patients, possibly also *Clostridium difficile*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0, and 140.8 mg/kg/day (about 0.4 to 34 times the human dose of 40 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 3.4 times the human dose of 40 mg/day on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week oral mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human lymphocyte chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test.

The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 34 times the human dose of 40 mg/day on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

13.2 Animal Toxicology and/or Pharmacology

Reproduction Studies

Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired

fertility or harm to the fetus due to esomeprazole [*see Pregnancy, Animal Data (8.1)*].

Juvenile Animal Study

A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole magnesium at doses of 70 to 280 mg/kg/day (about 17 to 57 times a daily oral human dose of 40 mg on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg/kg/day was observed when juvenile rats were administered esomeprazole magnesium from postnatal day 7 through postnatal day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 times a daily oral human dose of 40 mg on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

14 CLINICAL STUDIES

14.1 Acid Suppression in Gastroesophageal Reflux Disease (GERD)

Four multicenter, open-label, two-period crossover studies were conducted to compare the pharmacodynamic efficacy of the intravenous formulation of esomeprazole (20 mg and 40 mg) to that of esomeprazole delayed-release capsules at corresponding doses in patients with symptoms of GERD, with or without erosive esophagitis. The patients (n=206, 18 to 72 years old; 112 female; 110 Caucasian, 50 Black, 10 Asian, and 36 Other Race) were randomized to receive either 20 or 40 mg of intravenous or oral esomeprazole once daily for 10 days (Period 1), and then were switched in Period 2 to the other formulation for 10 days, matching their respective dose level from Period 1. The intravenous formulation was administered as a 3-minute injection in two of the studies, and as a 15-minute infusion in the other two studies. Basal acid output (BAO) and maximal acid output (MAO) were determined 22-24 hours post-dose on Period 1, Day 11; on Period 2, Day 3; and on Period 2, Day 11. BAO and MAO were estimated from 1-hour continuous collections of gastric contents prior to and following (respectively) subcutaneous injection of 6 mcg/kg of pentagastrin.

In these studies, after 10 days of once daily administration, the intravenous dosage forms of esomeprazole 20 mg and 40 mg were similar to the corresponding oral dosage forms in their ability to suppress BAO and MAO in these GERD patients (see table below).

There were no major changes in acid suppression when switching between intravenous and oral dosage forms.

Table 5

Mean (SD) BAO and MAO measured 22-24 hours post-dose following once daily oral and intravenous administration of esomeprazole for 10 days in GERD patients with or without a history of erosive esophagitis

Study	Dose in mg	Intravenous Administration Method	BAO in mmol H ⁺ /h		MAO in mmol H ⁺ /h	
			Intravenous	Oral	Intravenous	Oral
1 (N=42)	20	3-minute injection	0.71 (1.24)	0.69 (1.24)	5.96 (5.41)	5.27 (5.39)
2 (N=44)	20	15-minute infusion	0.78 (1.38)	0.82 (1.34)	5.95 (4.00)	5.26 (4.12)
3 (N=50)	40	3-minute injection	0.36 (0.61)	0.31 (0.55)	5.06 (3.90)	4.41 (3.11)
4 (N=47)	40	15-minute infusion	0.36 (0.79)	0.22 (0.39)	4.74 (3.65)	3.52 (2.86)

16 HOW SUPPLIED/STORAGE AND HANDLING

Esomeprazole sodium for Injection is supplied as a freeze-dried powder containing 40 mg of esomeprazole per single-use vial.

NDC 16729-252-69 one carton containing 10 vials of Esomeprazole sodium for Injection (each vial contains 40 mg of esomeprazole).

NDC 16729-252-66 one carton containing 1 vial of Esomeprazole sodium for Injection (each vial contains 40 mg of esomeprazole).

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]. Protect from light. Store in carton until time of use.

Following reconstitution and administration, discard any unused portion of esomeprazole solution.

17 PATIENT COUNSELING INFORMATION

- Advise patients to let their healthcare provider know if they are taking, or begin taking other medications, because Esomeprazole sodium for Injection can

interfere with antiretroviral drugs and drugs that are affected by gastric pH changes [*see Drug Interactions (7)*].

- Let patients know that antacids may be used while taking Esomeprazole sodium for Injection.
- Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea [*see Warnings and Precautions (5.4)*].
- Advise patients to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany as these may be signs of hypomagnesemia [*see Warnings and Precautions (5.7)*].

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