Natrapharm

Rx

Esomeprazole

Peprazom® IV

40mg Powder for Solution
for Injection (IV)

Pharmacologic Category: Proton Pump Inhibitor

Formulation:
Each vial contains:
Esomeprazole (as sodium) 40mg

Indications:
Esomeprazole (Peprazom IV) 40 mg Powder for Solution for Injection is indicated for:

Adults:
- Gastric antisecretory treatment when the oral route is not possible, such as:
  * Gastroesophageal reflux disease (GERD) in patients with esophagitis and/or severe symptoms of reflux.
  * Healing of gastric ulcers associated with NSAID therapy.
  * Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk

- Prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

Children and adolescents aged 1-18 years:
- Gastric antisecretory treatment when the oral route is not possible, such as:
* Gastroesophageal reflux disease in patients with erosive reflux esophagitis and/or severe symptoms of reflux.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Site and mechanism of action
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 5 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 GERD patients. The effect is similar irrespective of whether esomeprazole is administered orally or intravenously.

Using AUG as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown after oral administration of esomeprazole.

During intravenous administration of 80 mg esomeprazole as a bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/h for 23.5 hours, intragastric pH above 4, and pH above 6 was maintained for a mean time of 21 hours, and 11-13 hours, respectively, over 24 hours in healthy subjects.

Therapeutic effects of acid Inhibition
Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after 4 weeks, and in 93% after 8 weeks of oral treatment.

In a randomized, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10 % respectively) were randomized to receive esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72 hour period, all patients received open-label 40 mg oral esomeprazole for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the esomeprazole treated group compared to 10.3% for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the esomeprazole treated versus the placebo treated group was 7. 7% vs 13.6%.

Other effects related to acid inhibition
During treatment with antisecretory drugs serum gastrin increases in response to the decreased acid secretion.

Chromogranin A (CgA) also increases due to decreased gastric acidity.

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 orally administered esomeprazole.
During long-term oral treatment with antisecretory drugs gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

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

Paediatric population
In a placebo-controlled study (98 patients aged 1-11 months) efficacy and safety in patients with signs and symptoms of GERD were evaluated. Esomeprazole 1 mg/kg once daily was given orally for 2 weeks (open-label phase) and 80 patients were included for an additional 4 weeks (double blind, treatment-withdrawal phase). There was no significant difference between esomeprazole and placebo for the primary endpoint time to discontinuation due to symptom worsening.

In a placebo-controlled study (52 patients aged < 1 month) efficacy and safety in patients with symptoms of GERD were evaluated. Esomeprazole 0.5 mg/kg once daily was given orally for a minimum of 10 days. There was no significant difference between esomeprazole and placebo in the primary endpoint, change from baseline of number of occurrences of symptoms of GERD.

Results from the paediatric studies further show that 0.5 mg/kg and 1.0 mg/kg esomeprazole in < 1 month old and 1 to 11 month old infants, respectively, reduced the mean percentage of time with intraoesophageal pH < 4.

The safety profile appeared to be similar to that seen in adults.

In a study in paediatric GERD patients (<1 to 17 years of age) receiving long-term PPI treatment, 61% of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or carcinoid tumours.

Pharmacokinetic properties

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

Metabolism and excretion
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). 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 CYP2G19 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. Total exposure (AUC) 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 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.

Following repeated doses of 40 mg administered as intravenous injections, the mean peak plasma concentration is approx. 13.6 micromol/L. The mean peak plasma concentration after corresponding oral doses is approx. 4.6 micromol/L. A smaller increase (of approximately 30%) can be seen in total exposure after intravenous administration compared to oral administration. There is a dose-linear increase in total exposure following intravenous administration of esomeprazole as a 30-minute infusion (40 mg, 80 mg or 120 mg) followed by a continuous infusion (4 mg/h or 8 mg/h) over 23.5 hours.

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.

Special patient populations
Approximately 2.9±1.5% of the population lacks a functional CYP2C19 enzyme and is called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg oral esomeprazole, the mean total exposure was approximately 100% higher in poor metabolisers than in subjects with a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. Similar differences have been seen for intravenous administration of esomeprazole. These findings have no implications for the posology of esomeprazole.

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

Following a single oral dose of 40 mg esomeprazole the mean total exposure is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. Similar differences have been observed for intravenous administration of esomeprazole. These findings have no implications for the posology of esomeprazole.

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the total exposure of esomeprazole. Therefore, a maximum dose of 20 mg should not be exceeded in GERD patients with severe dysfunction. For patients with bleeding ulcers and severe liver impairment, following an initial bolus dose of 80 mg, a maximum continuous intravenous infusion dose of 4 mg/h for 71.5 hours may be sufficient. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

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.

Paediatric population
In a randomized, open-label, multi-national, repeated dose study, esomeprazole was given as a once-daily 3-minute injection over four days. The study induded a total of 59 paediatric patients 0 to 18 years old of which 50 patients (7 children in the age group 1 to 5 years) completed the study and were evaluated for the pharmacokinetics of esomeprazole.

The table below describes the systemic exposure to esomeprazole following the intravenous administration as a 3-minute injection in paediatric patients and adult healthy subjects. The values in the table are geometric means (range). The 20 mg dose for adults was given as a 30-minute infusion. The Css, max was measured 5 minutes post-dose in all paediatric groups and 7 minutes post-dose in adults on the 40 mg dose, and after stop of infusion in adults on the 20 mg dose.

Age group	Dose group	AUC (μmol*h/l)	Css, max (μmol/l)
0-1 month*	0.5 mg/kg (n=6)	7.5 (4.5-20.5)	3.7 (2.7-5.8)
1-11 months*	1.0 mg/kg (n=6)	10.5 (4.5-22.2)	8.7 (4.5-14.0)
1-5 years	10 mg (n=7)	7.9 (2.9-16.6)	9.4 (4.4-17.2)
6-11 years	10 mg (n=8)	6.9 (3.5-10.9)	5.6 (3.1-13.2)
	20 mg (n=8)	14.4 (7.2-42.3)	8.8 (3.4-29.4)
	20 mg (n=6)**	10.1 (7.2-13.7)	8.1 (3.4-29.4)
12-17 years	20 mg (n=6)	8.1 (4.7-15.9)	7.1 (4.8-9.0)
	40 mg (n=8)	17.6 (13.1-19.8)	10.5 (7.8-14.2)
Adults	20 mg (n=22)	5.1 (1.5-11.8)	3.9 (1.5-6.7)
	40 mg (n=41)	12.6 (4.8-21.7)	8.5 (5.4-17.9)

* A patient in the age group 0 up to 1 month was defined as a patient with a corrected age of ≥32 complete weeks and <44 complete weeks, where corrected age was the sum of the gestational age and the age after birth in complete weeks.
A patient in the age group 1 to 11 months had a corrected age of_ 44 complete weeks.

** Two patients excluded, 1 most likely a CYP2C19 poor metaboliser and 1 on concomitant treatment with a CYP3A4 inhibitor.
Model based predictions indicate that Css,max following intravenous administration of esomeprazole as a 10-minute, 20-minute and 30-minute infusions will be reduced by on average 37% to 49%, 54% to 66% and 61% to 72%, respectively, across all age and dose groups compared to when the dose is administered as a 3-minute injection.

Dosage and Mode of Administration:
Adults:
Gastric antisecretory treatment when the oral route is not possible:
Patients who cannot take oral medication may be treated parenterally with 20-40mg once daily. Patients with reflux esophagitis should be treated with 40 mg once daily. Patients treated symptomatically for reflux disease should be treated with 20 mg once daily.

For healing of gastric ulcers associated with NSAID therapy the usual dose is 20 mg once daily. For prevention of gastric and duodenal ulcers associated with NSAID therapy, patients at risk should be treated with 20 mg once daily.

Usually the intravenous treatment duration is short and transfer to oral treatment should be made as soon as possible.

Prevention of rebleeding of gastric and duodenal ulcers:
Following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. 80 mg should be administered as a bolus infusion over 30 minutes, followed by a continuous intravenous infusion of 8mg/h given over 3 days (72 hours).

The parenteral treatment period should be followed by oral-acid-suppression therapy.

Impaired renal function:
Dose 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.

Impaired hepatic function:
GERD: Dosage adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20 mg Esomeprazole should not be exceeded.

Bleeding ulcers: Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, following an initial bolus dose of 80 mg Esomeprazole for infusion, a continuous intravenous infusion dose of 4mg/h for 71.5 hours may be sufficient.

Elderly:
Dose adjustment is not required in the elderly.

Pediatric population (children and adolescent aged 1-18 years):
Gastric antisecretory treatment when the oral route is not possible:
Patients who cannot take oral medication may be treated parenterally once daily, as a part of a full treatment period for GERD (see doses in table below).

Usually the intravenous treatment duration should be short and transfer to oral treatment should be made as soon as possible.

Recommended intravenous doses of Esomeprazole:

Age group	Treatment of erosive reflux esophagitis	Symptomatic treatment of GERD
1- 11 years	Weight < 20 kg: 10 mg once daily Weight ≥20kg: 10 mg or 20 mg once daily	10 mg once daily
12 - 18 years	40 mg once daily	20 mg once daily

Instructions for use and handling, and disposal (if appropriate)
The reconstitution solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear solution should be used. Do not use if any parlides are present in the reconstituted solution. For single use only.

If the entire reconstituted content of the vial is not required any unused solution should be discarded in accordance with local requirements.

Injection 40 mg
A solution for injection (8 mg/ml) is prepared by adding 5 ml of 0.9% sodium chloride for intravenous use to the esomeprazole 40 mg vial.

The reconstituted solution for injection is clear and colourless to very slightly yellow.

Infusion 40 mg
A solution for infusion is prepared by dissolving the content of one vial with esomeprazole 40 mg in up to 100 ml of 0.9% sodium chloride for intravenous use.

The reconstituted solution for injection is clear and colourless to very slightly yellow.

Infusion 80 mg
A solution for infusion is prepared by dissolving the contents of two vials of esomeprazole 40 mg in up to 100 ml of 0.9% sodium chloride for intravenous use.

The reconstituted solution for infusion is clear and colourless to very slightly yellow.

Method of Administration:
Injection:

40 mg dose	- 5 ml of the reconstituted solution (8mg/ml) should be given as an intravenous injection over a period of at least 3 minutes.
20 mg dose	- 2.5 ml or half of the reconstituted solution (8mg/ml) should be given as an intravenous injection over a period of approximately 3 minutes. Any unused solution should be discarded.
10 mg dose	- 1.25 ml of the reconstituted solution (8mg/ml) should be given as an intravenous injection over a period of at least 3 minutes. Any unused solution should be discarded.

Infusion:

40 mg dose	- The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.
20 mg dose	- half of the reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Any unused solution should be discarded.
10 mg dose	- a quarter of the reconstituted solution should be given as an intravenous infusion
80 mg bolus dose	- The reconstituted solution should be given as a continuous intravenous infusion over 30 minutes.
8mg/h dose	- The reconstituted solution should be given as a continuous intravenous infusion over a period of 71.5 hours (calculated rate of infusion of 8mg/h)

Contraindications:
Hypersensitivity to the active substance esomeprazole or to other substituted benzimidazoles or to any of the excipients of this medicinal product.

Esomeprazole should not be used concomitantly with nelfinavir.

Warnings and Precautions:
In the presence of any alarm symptoms (e.g. 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 Esomeprazole may alleviate symptoms and delay diagnosis.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Co-administration of esomeprazole with atazanavir is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Hypomagnesemia
Severe hypomagnesemia has been reported in patients treated with PPIs like esomeprazole for at least 3 months, and in most cases for a year. Serious manifestations of hypomagnesemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesemia improved after magnesium replacement and discontinuation of the PPI.

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

Risk of hip, wrist and spine fracture:
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in the presence of other recognized risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

This medicine contains less than 1 mmol (23mg) of sodium per vial, so essentially "sodium-free".

Esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.
Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolized through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

Interference with laboratory test:
Increased CgA level may interfere with investigations for neuroendocrine tumors. To avoid this interference, esomeprazole treatment should be temporarily stopped for a least five days before CgA measurements.

Interaction with other medicinal products and other forms of Interaction:

Interaction studies have only been perfonned in adults:

Effect of esomeprazole on the pharmacokinetics of other drugs:

Medicinal products with pH dependent absorption:
The decreased intragastric acidity during treatment with esomeprazole 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 ketoconazole and itraconazole can decrease and the absorption of 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 10 subjects). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Omeprazole has been reported to interact with some protease inhibitors. 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 protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19. For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Coadministration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavirexposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, C_{max} and C_{min} by 36-39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite MB was reduced by 75-92%. For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg qd). Treatment with omeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg qd had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg qd had no effect on the exposure of lopinavir (with concomitant ritonavir). Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

Drugs metabolised by CYP2C19
Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed. Concomitant oral administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. Concomitant oral administration of 40 mg esomeprazole and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC, by 15% and 41%, respectively.

Concomitant oral administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing of oral esomeprazole, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarin derivatives.

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19 Omeprazole, given in doses of 40 mg to healthy subjects in a crossover study, increased Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

In healthy volunteers, concomitant oral administration of 40 mg esomeprazole and cisapride resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) 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.

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

No *in vivo* interaction studies have been perfom1ed with the high dose iv regimen (80mg+8mg/h). The effect of esomeprazole on drugs metabolised by CYP2C19 may be more pronounced during this regimen, and patients should be monitored dosely for adverse effects, during the 3-day i.v. treatment period.

In a crossover clinical study, clopidogrel (300 mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47% (24 hours) and 30% (Day 5) when clopidogrel and omeprazole were administered together. In another study it was shown that administering clopidogrel and omeprazole at different times did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19. Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from observational and clinical studies.

Unknown mechanism
When given together with PPIs, 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.

Effects of other drugs on the pharmacokinetics of esomeprazole:
Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC, by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

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.

Pregnancy and lactation
For esomeprazole limited data on exposed pregnancies are available. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing Esomeprazole to pregnant women.

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore Esomeprazole should not be used during breast-feeding.

Undesirable effects:
The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole administered orally or intravenously and post-marketing when administered orally. The reactions are classified according to frequency: very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare ≥ 1/10,000 to <1/1,000; very rare <1/10,000; not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: Leukopenia, thrombocytopenia
Very rare: Agranulocytosis, pancytopenia
Immune system disorders
Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders
Uncommon: Peripheral oedema
Rare: Hyponatraemia
Frequency not known: hypomagnesaemia.
Psychiatric disorders
Uncommon: Insomnia
Rare: Agitation, confusion, depression
Very rare: Aggression, hallucinations
Nervous system disorders
Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance
Eye disorders
Uncommon: Blurred vision
Ear and labyrinth disorders
Uncommon: Vertigo
Respiratory thoracic and mediastinal disorders
Rare: Bronchospasm
Gastrointestinal disorders
Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Uncommon: Dry mouth
Rare: Stomatitis, gastrointestinal candidiasis
Frequency not known: Microscopic colitis
Hepatobiliary disorders
Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders
Common: Administration site reactions*
Uncommon: Dermatitis, pruritus, rash, urticaria
Rare: Alopecia, photosensitivity
Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal connective tissue and bone disorders
Uncommon: Fracture of the hip, wrist or spine ralgia, 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, increased sweating

*Administration site reactions have mainly been observed in a study with high-dose exposure over 3 days (72 hours).

Irreversible visual impairment has been reported in isolated cases critically ill patients who have received omeprazole (the racemate intravenous injection, especially at high doses, but no cause relationship has been established.

Paediatric population
A randomised, open-label, multi-national study was conducted evaluate the pharmacokinetics of repeated intravenous doses for days of once daily esomeprazole in paediatric patients 0 to 18 year old. A total of 57 patients (8 children in the age group 1-5 years) were included for safety evaluation. The safety results are consistent with the known safety profile of esomeprazole, and no new safety signal were identified.

Overdose
There is very limited experience to date with deliberate overdose. The symptoms described in connection with an oral dose of 280 mg were gastrointestinal symptoms and weakness. Single oral doses of 80 mg esomeprazole and intravenous doses of 308 mg esomeprazole over 24 hours were uneventful. No specific antidote is known. Esomeprazole is extensively plasma 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.

Storage:
Store below 30°C. Store in the original package, in order to protect from light.

Availability:
Type I colorless vial, closed with a stopper and sealed with an aluminum cap in box of 1's.

Caution: Foods, Drugs, Devices and Cosmetics Act prohibit dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Registration Number: DR-XY45662
Date of First Authorization: Nov 2016
Revision Date: Nov 2016

Manufactured by:
Laboratorios Norman S.A.
Ronda de Valdecarrizo,
6 - 28760 Tres Cantos,
Madrid, Spain

Imported and Distributed by:
Natrapharm, Inc.
The Patriot Bldg.
Km 18 West Service Road, SLEX,
Paranaque City

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