For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ADPTOR

Esomeprazole Sodium for Injection 40mg/Vial

QUALITATIVE AND QUANTITATIVE COMPOSITION
Esomeprazole Sodium for Injection 40mg/Vial
Each Vial contains:
Esomeprazole Sodium eq. to
Esomeprazole 40mg

PHARMACEUTICAL FORM
Powder for Solution for Injection/Infusion
White to off white, porous cake or powder.

CLINICAL PARTICULARS
Therapeutic indications
Esomeprazole Sodium Injection is indicated for:
Adults
- gastric antisecretory treatment when the oral route is not possible, such as:
- gastroesophageal reflux disease (GORD) 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 (GORD) in patients with erosive reflux esophagitis and/or severe symptoms of reflux.

Posology and method of administration
Posology
Adults
Gastric antisecretory treatment when the oral route is not possible
Patients who cannot take oral medication may be treated parenterally with 20–40 mg once daily. Patients with reflux oesophagitis 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 8 mg/h given over 3 days (72 hours).
The parenteral treatment period should be followed by oral acid-suppression therapy.

Patients with renal impairment
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.

Patients with hepatic impairment
GORD: Dose 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 4 mg/h for 71.5 hours may be sufficient.

Older people
Dose adjustment is not required in the elderly.

Method of administration
For preparation of reconstituted solution, see section 'Special precaution for disposal and other handling'.

Injection
40 mg dose
5 ml of the reconstituted solution (8 mg/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 (8 mg/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.
80 mg bolus dose
The reconstituted solution should be given as a continuous intravenous infusion over 30 minutes.

8 mg/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 8 mg/h. See section 'Shelf-life' for shelf-life of the reconstituted solution).

Paediatric population
Posology
Children and adolescents 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 GORD (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 erosive reflux oesophagitis	Symptomatic treatment of GORD
1-11 Years	Weight <20 kg: 10 mg once daily Weight ≥20 kg: 10 mg or 20 mg once daily	10 mg once daily
12-18 Years	40 mg once daily	20 mg once daily

Method of administration
For preparation of reconstituted solution, see section 'Special precaution for disposal and other handling'.
Injection
40 mg dose
5 ml of the reconstituted solution (8 mg/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 (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes. Any unused solution should be discarded.
10 mg dose
1.25 ml of the reconstituted solution (8 mg/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 over a period of 10 to 30 minutes. Any unused solution should be discarded.

Contraindications
Hypersensitivity to the active substance esomeprazole or to other substituted benzimidazoles or to any of the excipients listed in section 'List of excipients'.
Esomeprazole should not be used concomitantly with nelfinavir.

Special warnings and precautions for use
In the presence of any alarm symptom (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.
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 metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia 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 hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.
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 presence of other recognised 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.
Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least five days before CgA measurements.
This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e essentially "sodium free"

Interaction with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults.

Effects of esomeprazole on the pharmacokinetics of other drugs
Medicinal products with pH dependent absorption
Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib 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 ten 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. Co-administration 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 atazanavir exposure. 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 M8 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 AUCby 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 coumarine derivatives.
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.
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 performed with the high dose intravenous regimen (80 mg + 8 mg/h). The effect of esomeprazole on drugs metabolised by CYP2C19 may be more pronounced during this regimen, and patients should be monitored closely for adverse effects during the 3-day intravenous treatment period.
Results from studies in healthy subject have shown a pharmacokinetic(PK)/pharmacodynamic(PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and eomeprazole (40 mg p.o.daily) Resulting in decreased exposure to the active metabolite of clopidogrel by 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggression by an average of 14%.
When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolites of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.
Inconsistent data on the clinical implications of this PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

Unknown mechanism
Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.
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 CYP 3A4 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.

Fertility, pregnancy and lactation
Pregnancy
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/foetal 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.
Breast-feeding
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.
Fertility
There are no data on the effects of esomeprazole on human fertility.

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

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
Not known: Hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.

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
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 and connective tissue disorders
Uncommon: Fracture of the hip, wrist or spine
Rare: Arthralgia, myalgia
Very rare: Muscular weakness

Renal and urinary disorders
Very rare: Interstitial nephritis; in some patients renal failure has been reported concomitantly
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 of critically ill patients who have received omeprazole (the racemate) intravenous injection, especially at high doses, but no causal relationship has been established.

Paediatric population
A randomised, open-label, multi-national study was conducted to evaluate the pharmacokinetics of repeated intravenous doses for 4 days of once daily esomeprazole in paediatric patients 0 to 18 years 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 signals were identified.

Overdose
Symptoms:
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.
Management:
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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Drug for peptic ulcer and gastro-oesophageal reflux disease - Proton pump inhibitor
ATC Code: A02B C05
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 GORD patients. The effect is similar irrespective of whether esomeprazole is administered orally or intravenously.
Using AUC 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 oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after 4 weeks, and in 93% after 8 weeks of oral treatment.
In a randomised, 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 randomised 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 medicinal product, serum gastrin increases in response to the decreased acid secretion. Chromogranin A (CgA) also increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped at least 5 days before CgA measurement. If CgA and gastrin levels have not normalised after 5 days, measurements should be repeated 14 days after cessation of esomeprazole treatment.
An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long-term treatment with orally administered esomeprazole. The findings are considered to be of no clinical significance.
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* and, 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 GORD 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 GORD 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 GORD.
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 intra-oesophageal pH < 4.
The safety profile appeared to be similar to that seen in adults.
In a study in paediatric GORD 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.

Biotransformation and elimination
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 CYP2C19 enzyme, extensive metabolisers.
Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once daily dosing. 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 approx 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 lack a functional CYP2C19 enzyme and are 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 elderly 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 GORD 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 randomised, open-label, multi-national, repeated dose study, esomeprazole was given as a once-daily 3-minute injection over four days. The study included 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 $C_{ss,max}$ 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	10mg (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 $C_{ss,max}$ 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.

PHARMACEUTICAL PARTICULARS
List of excipients
Disodium EDTA
Sodium hydroxide (for pH adjustment)

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 'Special precautions for disposal and other handling'.

Shelf life
Unopened vial: 2 years

Shelf-life after reconstitution
Chemical and physical stability of reconstituted solution has been demonstrated for 12 hours at 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Special precautions for storage
Keep the vial in outer carton, in order to protect from light. Vials can however, be stored exposed to normal indoor light outside the box for up to 24 hours. Store below 25°C.
For storage conditions after reconstitution of the medicinal product, see section 'Shelf life'.

Pack sizes:
1 vial

Special precautions for disposal and other handling
The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear solution should be used. 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.
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.

Manufactured By:
Intas Pharmaceuticals Ltd.,
Plot no.- 457 - 458, Village-Matoda,
Bavla road, Dist.-Ahmedabad,
Gujarat, India.

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