Protas®

Esomeprazole INN

COMPOSITION

Protas® 20 tablet: Each enteric coated tablet contains Esomeprazole INN 20 mg as Esomeprazole Magnesium Trihydrate.
Protas® 40 tablet: Each enteric coated tablet contains Esomeprazole INN 40 mg as Esomeprazole Magnesium Trihydrate.
Protas® 40 IV Injection: Each vial contains Esomeprazole 40 mg (as lyophilized powder of Esomeprazole Sodium INN) and each ampoule contains 5 ml of 0.9% Sodium Chloride Injection BP.

PHARMACOLOGY

Pharmacokinetics

Absorption

Absorption of esomeprazole in healthy subjects results in peak plasma levels occurring 1 to 2 hours after dosing. The systemic bioavailability is 64% after a single 40 mg dose and 89% after repeated once daily oral administration (40 mg for 5 days). The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound and optically stable in vivo, with negligible inversion to the other isomer.

A pharmacokinetic profile of esomeprazole was studied in 36 patients with symptomatic GERD after repeated once daily administration of 20 mg and 40 mg (Table 1).

Pharmacokinetic Parameters of ESOMEPRAZOLE Following Oral Dosing for 5 days		
Parameter	**Esomeprazole** 40 mg	**Esomeprazole** 20 mg
AUC (mmol*h/L)	12.6	4.2
Coefficient of variation	42%	59%
Cmax (mmol/L)	4.7	2.1
T_{max} (h)	1.6	1.6
$t_{1/2}$ (h)	1.5	1.2
Values represent the geometric mean, except the T_{max}, which is the arithmetic mean.		

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

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 mol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is completely metabolized by the cytochrome P-450 system, mainly in the liver (via CYP 2C19 and CYP 3A4). The major metabolites of esomeprazole (hydroxy and desmethyl metabolites) have no effect on gastric acid secretion. The CYP 2C19 isozyme, which is involved in the metabolism of all available proton pump inhibitors, exhibits polymorphism. Some 3% of Caucasians and 15-20% of Asians lack CYP 2C19 and are termed "poor metabolizers." At steady state (40 mg for 5 days), the ratio of AUC in poor metabolizers to AUC in the rest of the population is approximately 2. Dosage adjustment of **Protas®** based on CYP 2C19 status is not necessary.
Almost 80% of an oral dose of esomeprazole is excreted as metabolites in urine with the remainder recovered in feces. Less than 1% of the parent drug is found in urine. Total recovery from urine and feces is 92 to 96% within 48 hours of a single oral dose.

Excretion

The plasma elimination half-life of esomeprazole is approximately 1-1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

Pharmacodynamics

Mechanism of Action

Esomeprazole accumulates in the acidic environment of the parietal cells after absorption, where it is converted into the active form. This active sulphenamide specifically binds the H+, K+-ATPase (proton pump), to block the final step in acid production, thus reducing gastric acidity. Esomeprazole is effective in the inhibition of both basal acid secretion and stimulated acid secretion.
In healthy male subjects (N=12), repeated administration with 20 mg **Protas®** once daily for 5 days, decreased mean peak acid output after pentagastrin stimulation by 90% when measured 6 to 7 hours after dosing.
The effect of antisecretory therapy can be predicted from the duration of suppression of intragastric acidity to above pH 4.0 achieved by each drug regimen, and the length of treatment.

Antisecretory Activity

The antisecretory activity of esomeprazole magnesium was studied in patients with symptomatic gastroesophageal reflux disease. **Protas®** 20 and 40 mg tablets were administered over 5 days and the proportion of time over 24 hours was assessed on Day 5, as shown in the following table:

Effect on Intragastric pH on Day 5 (N=36)		
Parameter	**Esomeprazole** 40 mg	**Esomeprazole** 20 mg
% Time Gastric	70%*	53%
pH >4† (Hours)	(16.8 h)	(12.7 h)
Coefficient of variation	26%	37%
Median 24 Hour pH	4.9*	4.1
Coefficient of variation	16%	27%
† GASTRIC PH WAS MEASURED OVER A 24-HOUR PERIOD		
*P< 0.01 Esomeprazole 40 mg vs Esomeprazole 20 mg		

Eradication of Helicobacter pylori
Infection with *Helicobacter pylori (H. pylori)* is associated with peptic ulcer disease and is a major factor in the development of gastritis. Approximately 90 to 100% of patients with duodenal ulcers, and 80% of patients with gastric ulcer, are infected with *H. pylori.* Treatment with **Protas®** alone has been shown to suppress, but not eradicate *H. pylori.* Eradication of *H. pylori* with triple therapy consisting of **Protas®** and clarithromycin/ amoxicillin for seven days is associated with healing and improvement of symptoms of duodenal ulcers.

INDICATION, DOSAGE AND ADMINISTRATION

Recommended Adult Dosage Schedule of **Protas®** tablet

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once daily for 4 to 8 weeks*
Maintenance of Healing of Erosive Esophagitis	20 mg	Once Daily **
Symptomatic Gastroesophageal Reflux	20 mg	Once daily for 4 weeks ***
***H. pylori* Eradication to reduce the Risk of Duodenal Ulcer Recurrence**		
Triple Therapy :		
Protas®	40 mg	Once daily for 10 Days
Amoxicillin	1000 mg	Twice daily for 10 Days
Clarithromycin	500 mg	Twice daily for 10 Days

Injection :

Duodenal ulcer, gastric ulcer, gastrointestinal lesions refractory to H2 blockers, Zollinger-Ellison syndrome	40 mg per day intravenously
Reflux esophagitis	20-40 mg per day intravenously

Paediatric use (12 years and older):
Short term treatment of GERD: 20 mg or 40 mg once daily for up to 8 weeks.
* The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4-8 weeks, an additional 4-8 weeks treatment may be considered.
** Controlled studies did not extend beyond six months.
*** If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

DIRECTION FOR USE OF IV INJECTION

Esomeprazole lyophilized powder and 0.9% Sodium Chloride Injection is for intravenous administration only and must not be given by any other route. Esomeprazole injection 40 mg should be given as a slow intravenous injection. The solution for IV injection is obtained by adding 5 ml 0.9% Sodium Chloride Injection to the vial containing powder. After reconstitution the injection should be given slowly over a period of at least 3 minutes. Use only freshly prepared solution. The reconstituted solution may be stored at room temperature (up to 30°c) for a maximum 12 hours. Half of the IV injection should be used when 20 mg to be administered.

DIRECTION FOR USE OF IV INFUSION

Esomeprazole IV 40 mg should be given as an intravenous infusion over a period of 10 to 30 minutes. Esomeprazole IV should be reconstituted with 5 ml of 0.9% Sodium Chloride Injection and further diluted (admixed) with 5% Dextrose Injection or 0.9% Sodium Chloride Injection or Lactated Ringer's Injection to a final volume of 50 ml. The reconstituted solution may be stored at room temperature (up to 30°c) for a maximum 12 hours prior to dilution. The admixed solution may be stored at room temperature (up to 30°c) and must be used within 12 hours when reconstituted with 0.9% Sodium Chloride Injection or Lactated Ringer's Injection and within 6 hours when reconstituted with 5% Dextrose Injection.

CONTRAINDICATION AND PRECAUTION

Esomeprazole is contraindicated in those patients who have known hypersensitivity to any component of the formulation.
Exclude the possibility of malignancy when gastric ulcer is suspected and before treatment for dyspepsia. When using in combination with antibiotic, refer to the prescribing information of the respective antibiotics.

SIDE EFFECT

Side effects reported with Esomeprazole include the following:

- Headache
- Diarrhoea
- Abdominal pain

USE IN PAEDIATRIC PATIENT

Safety and effectiveness have not yet been established in paediatric patients.

SPECIAL POPULATION

Geriatric : No dosage adjustment is necessary.
Renal Insufficiency : No dosage adjustment is necessary.
Hepatic Insufficiency : No dosage adjustment is necessary in patients with mild to moderate liver impairment. For patients with severe liver impairment a dose of 20 mg of **Protas®** should not be exceeded.
Gender: No dosage adjustment is necessary.

DRUG INTERACTION

Esomeprazole appears to be a selective inhibitor of the cytochrome P-450 mono-oxygenase system; there may be an effect on hepatic clearance, but there have been no reports to date of clinically relevant interactions. There is some uncertainty over the effect of Esomeprazole on the oral combined contraceptive pill. Further assessment is currently underway. Physiological changes similar to those found with omeprazole are likely to take place because of the reduction in gastric acid, which is likely to influence the bacterial colonization of the stomach and duodenum and also vitamin B_{12} absorption.

WARNING

In the presence of any alarm symptom (e.g., significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis or melena) and/or when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No information is available on the effects of higher doses in man, and specific recommendations for treatment cannot be given. No specific antidote is known. Esomeprazole is extensively protein-bound and is therefore not readily dialyzable. Treatment should be symptomatic and general supportive measures should be utilized.
The maximum non-lethal oral dose in male and female rats ranged from 240 to 480 mg/kg.
When used in combination with antibiotics, the Prescribing Information/Product Monograph for those antibiotics should be consulted.

USE IN PREGNANCY AND LACTATION

US FDA Pregnancy Category - 'B'
Teratology studies have been performed in animals and have revealed no evidence of impaired fertility or harm to the fetus due to Esomeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Because Esomeprazole is likely to be excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

STORAGE CONDITION

Store below 30°C. Protect from light and moisture. Keep out of children's reach.

HOW SUPPLIED

Protas® 20 tablet : Box containing 2 x 6 / 5 x 6 / 1 x 10 / 2 x 10 / 3 x 10 / 4 x 10 / 5 x 10 / 10 x 10 tablets in blister pack.
Protas® 40 tablet : Box containing 2 x 6 / 5 x 6 / 1 x 10 / 2 x 10 / 3 x 10 / 4 x 10 / 5 x 10 / 10 x 10 tablets in blister pack.
Protas® 40 IV Injection: Each box contains one vial of lyophilized Esomeprazole 40 mg, one ampoule of 5 ml 0.9% Sodium Chloride Injection and one sterile disposable syringe (5 ml).

SQUARE