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Intravenous Esomeprazole

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Contents

Abstract

▲ The proton pump inhibitor esomeprazole comprises the *S*-isomer of omeprazole. An intravenous formulation of the drug has been developed for use in patients not able to take oral drugs.

▲ The level of gastric acid control was similar with intravenous and oral esomeprazole in two studies in healthy volunteers receiving 20 or 40mg once daily for 5 days. In addition, a similar level of gastric acid control occurred with intravenous esomeprazole 40mg administered by infusion or injection once daily for 10 days.

▲ In healthy volunteers, intravenous esomeprazole provided faster and more effective gastric acid control than intravenous pantoprazole (40mg once daily for 5 days). In addition, control of basal and pentagastrin-stimulated gastric acid secretion was better with intravenous esomeprazole 40mg than with intravenous omeprazole 40mg (single-dose study).

▲ Healing rates at 4 weeks were ≈80% in a well designed study in patients with erosive oesophagitis (n = 246) who received esomeprazole 40mg once daily intravenously (by injection or infusion) or orally. Intravenous therapy was administered for the first week, after which all patients received oral esomeprazole.

▲ Intravenous esomeprazole was generally well tolerated in patients with erosive oesophagitis, with a tolerability profile similar to that of the oral formulation.

Features and properties of intravenous (IV) esomeprazole (Nexium® i.v.)	
Indication	
Treatment of gastro-oesophageal reflux disease (GORD) in patients with reflux oesophagitis and/or severe reflux symptoms for whom oral therapy is not appropriate	
Mechanism of action	
Proton pump inhibitor	Inhibits gastric acid secretion
Dosage and administration	
Recommended dosage	20mg (symptomatic GORD) or 40mg (oesophagitis)
Route of administration	IV infusion or injection
Frequency of administration	Once daily
Pharmacokinetic profile (20 or 40mg once daily for 5 days by IV infusion)	
Maximum plasma concentration	20mg: 3.86 μmol/L; 40mg: 7.51 μmol/L
Area under the plasma concentration-time curve	20mg: 5.11 μmol • h/L; 40mg: 16.21 μmol • h/L
Volume of distribution at steady-state	20mg: 15.13L
Systemic clearance	20mg: 11.3 L/h
Elimination half-life	20mg: 1.05h
Adverse events	
Most frequent	Headache, flatulence, nausea, diarrhoea, abdominal pain, constipation, dizziness/vertigo

Gastro-oesophageal reflux disease (GORD) is a common, often chronic, condition.[1] It includes a broad spectrum of disorders from heartburn to erosive oesophagitis to severe complications such as Barrett's oesophagus.[2] The development of the class of drugs known as proton pump inhibitors represents a major advance in the treatment of GORD.[3,4]

The proton pump inhibitor esomeprazole (Nexium®)[1] comprises the *S*-isomer of omeprazole and has pharmacological advantages over the racemic compound (reviewed by Scott et al.[5,6]). Oral esomeprazole is widely available and is indicated for the healing and maintenance treatment of erosive oesophagitis associated with GORD and the treatment of symptomatic GORD, as well as the eradication of *Helicobacter pylori* infection (in combination with antibacterials).

Oral medication may not be a suitable option in certain patient groups (e.g. hospitalised patients who are in the intensive care unit). An intravenous formulation of esomeprazole (Nexium® i.v.) has been developed for use in patients not able to take oral drugs. This profile focuses on the antisecretory activity and pharmacokinetics of intravenous esomeprazole as well as its clinical efficacy and tolerability in patients with erosive oesophagitis.

1. Pharmacodynamic Profile

Mechanism of Action

- The mechanism of action of esomeprazole is well established and has been reviewed previously.[5,6] Briefly, conversion of esomeprazole to its active form in gastric parietal cells results in inhibition of the H^+/K^+-ATPase enzyme (the proton pump).[5,6] Both basal and stimulated acid secretion are inhibited by esomeprazole.[7]

Antisecretory Activity

Five randomised crossover studies examined the effect of intravenous esomeprazole on gastric acid control.[8-12] Studies enrolled healthy volunteers (n = 23–41) and were of double-blind[9,10] or non-blind[8,11,12] design. Intravenous esomeprazole was administered as an infusion (over 15[11] or 30[8-10,12] minutes) or as a 3-minute injection.[10] In three studies, intragastric acid control was assessed over 24-hour periods at baseline[8-10] and on days 1 and 5[8,9] or days 1 and 10.[10] In a fourth study, comparing intravenous esomeprazole with intravenous pantoprazole, intragastric acid control was assessed during the first 4 hours and the entire 24 hours following drug administration on days 1 and 5.[11] Additional analyses[13] of this study[11] are also available. Most studies are available as abstracts and/or posters.[8-11]

- The level of gastric acid control was similar with intravenous and oral esomeprazole in two 5-day studies.[8,9] With intravenous and oral esomeprazole 20mg once daily, the mean amount of time spent with an intragastric pH >4 was 7.3 and 6.6 hours on day 1 and 11.9 and 12.3 hours on day 5; there was no significant difference between the administration routes at either timepoint (a mean 2.6 hours was spent with an intragastric pH >4 at baseline).[8]

- Median intragastric pH was 3.1 with intravenous esomeprazole 20 mg/day and 2.51 with oral esomeprazole 20 mg/day on day 1 and 3.96 and 3.94 on day 5 (median intragastric pH 1.61 at baseline).[8]

- In a study examining the use of intravenous and oral esomeprazole 40mg once daily, the time spent with an intragastric pH >4 favoured intravenous administration on day 1 (between-group difference 1.3 hours; 95% CI 0.3, 2.4 hours).[9] However, on day 5 the between-treatment difference was only 0.6 hours (95% CI −0.1, 1.4 hours).[9]

- A similar level of gastric acid control was achieved with intravenous esomeprazole 40mg administered once daily by injection or infusion for 10 days.[10] The mean percentage of time spent with an intragastric pH >4 with injection or infusion of esomeprazole was 32.3 and 33.1% on day 1 and 57.2 and 55.6% on day 10. The difference between administration routes (injection minus infusion) was

1 The use of trade names is for product identification purposes only and does not imply endorsement.

−0.8% (95% CI −4.0, 2.4) on day 1 and 1.6% (95% CI −1.7, 4.9) on day 10.

- Intravenous esomeprazole 40mg once daily provided faster and more effective gastric acid control than intravenous pantoprazole 40mg once daily.[11] On days 1 and 5, significantly more time was spent with an intragastric pH >4 and the median pH was significantly higher with esomeprazole than with pantoprazole during both the first 4 hours and the entire 24 hours following drug administration (figure 1).[11,13] Day 1 and 5 data concerning the first 4 hours post-dose were obtained from an additional retrospective analysis.[13]
- In addition, area under the H^+-time curve values were reduced from baseline (1004 mmol • h/L) to a significantly greater extent with intravenous esomeprazole than with intravenous pantoprazole. Values (assessed during the 24 hours post-dose) were 543 versus 769 mmol • h/L ($p < 0.05$) on day 1 and 192 versus 340 mmol • h/L ($p < 0.001$) on day 5.[13]
- Control of basal and pentagastrin-stimulated gastric acid secretion was better with a single intravenous infusion of esomeprazole 40mg than with a single intravenous infusion of omeprazole 40mg (figure 2).[12] The mean between-treatment difference favoured esomeprazole for basal acid output assessed at 3–5.5 hours (−0.4 mmol/h; 95% CI −0.8, 0.0) and 23–25.5 hours (−0.5 mmol/h; 95% CI −0.8, −0.2) and pentagastrin-stimulated acid output at 3–5.5 hours (−4.1 mmol/h; 97.5% CI −6.2, −1.9) and 23–25.5 hours (−4.3 mmol/h; 95% CI −7.1, −1.5).

Other Effects

- The manufacturer's prescribing information states that an increase in serum gastrin levels occurs during treatment with antisecretory drugs such as esomeprazole.[7] Increased numbers of enterochromaffin-like cells were seen in some patients receiving long-term treatment with oral esomeprazole and an increased frequency of gastric glandular cysts has also been reported in patients receiving long-term treatment with oral antisecretory drugs.[7] Data concerning the use of intravenous esomeprazole are not available.

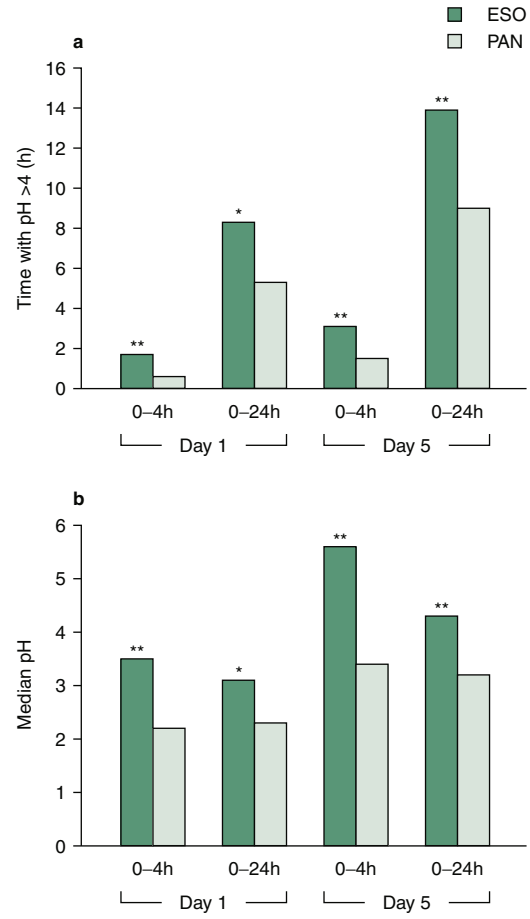

Fig. 1. Gastric acid control with intravenous (IV) esomeprazole (ESO) vs pantoprazole (PAN). In this randomised nonblind study, 25 healthy volunteers received 15-minute IV infusions of ESO and PAN 40mg once daily for 5 days each in a crossover manner.[11] The (**a**) time spent with pH >4 and (**b**) median pH were assessed on days 1 and 5, 0–4 and 0–24 hours after drug administration. Day 1 and 5 data concerning the first 4 hours post-dose were obtained from an additional retrospective analysis.[13] * $p < 0.001$, ** $p < 0.0001$ vs PAN.

2. Pharmacokinetic Profile

This section examines the pharmacokinetic profile of intravenous esomeprazole (usually administered by infusion over 30 minutes[8-10] although infusions over 10–30 minutes[14] and intravenous injection[10] were also assessed). Studies were of randomised crossover design and enrolled healthy volunteers (n = 24–41);[8-10,14] two studies were double-blind[9,10] and two were nonblind.[8,14] Stud-

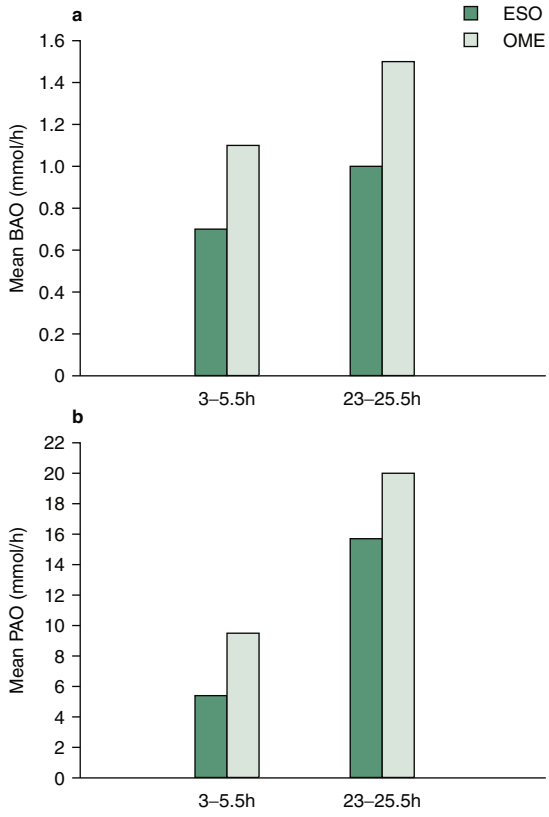

Fig. 2. Control of gastric acid secretion with intravenous (IV) esomeprazole (ESO) vs omeprazole (OME). In this randomised nonblind study, 23 healthy volunteers received single 30-minute IV infusions of ESO and OME 40mg in a crossover manner.[12] Mean (**a**) basal acid output (BAO) and (**b**) pentagastrin-stimulated acid output (PAO) were assessed 3–5.5 and 23–25.5 hours after drug administration. At baseline, mean BAO was 4.4 mmol/h and mean PAO was 34.0 mmol/h.

ies are available as abstracts and/or posters.[8-10,14] Data relating to oral esomeprazole and data from the manufacturer's prescribing information[7] are included where appropriate.

Absorption and Distribution

- As expected, the maximum plasma concentration (C_{max}) of intravenous esomeprazole 40mg increased as the infusion rate increased in a single-dose study.[14] Administration over 30, 20, 15 and 10 minutes resulted in mean C_{max} values of 5.16, 6.39, 6.67 and 7.57 μmol/L, respectively. In contrast, mean area under the plasma concentration-time curve (AUC) values were similar regardless of the infusion rate (7.07–7.38 μmol • h/L).
- C_{max} and AUC values were numerically higher with intravenous than with oral administration of esomeprazole 20[8] or 40mg[9] once daily (statistical analysis not reported); the increased systemic exposure reflects the lack of first-pass metabolism. With esomeprazole 20 mg/day, mean C_{max} was 3.32 and 0.78 μmol/L with intravenous and oral administration on day 1, and 3.86 and 1.57 μmol/L on day 5.[8] Mean C_{max} with esomeprazole 40 mg/day was 6.77 and 2.97 μmol/L with intravenous and oral administration on day 1, and 7.51 and 4.60 μmol/L on day 5.[9]
- Mean AUC values with esomeprazole 20 mg/day were 3.4 and 1.86 μmol • h/L with intravenous and oral administration on day 1, and 5.11 and 3.92 μmol • h/L on day 5.[8] With esomeprazole 40 mg/day, mean AUC values were 9.88 and 5.94 μmol • h/L with intravenous and oral administration on day 1, and 16.21 and 12.55 μmol • h/L on day 5.[9]
- Systemic exposure was increased with repeat administration of esomeprazole.[8,9] When this was observed with oral esomeprazole in an earlier study it was attributed to reduced systemic clearance and first-pass metabolism with repeat administration.[15]
- As expected, C_{max} was numerically higher when intravenous esomeprazole 40mg once daily was administered by injection (over 3 minutes) than by infusion (over 30 minutes) [statistical analysis not reported].[10] At day 10, mean C_{max} was 13.55 and 7.00 μmol/L with injection and infusion; mean AUC values were 12.58 and 10.96 μmol • h/L.
- The mean volume of distribution at steady state was 15.13L following 5 days' administration of intravenous esomeprazole 20 mg/day.[8] Esomeprazole is 97% protein bound and is chirally stable.[16]

Metabolism and Elimination

- Esomeprazole is metabolised extensively in the liver by two cytochrome P450 (CYP) isoenzymes to pharmacologically inactive metabolites.[16,17] CYP2C19 is responsible for the formation of hydroxy and 5-*O*-desmethyl metabolites and CYP3A4 is responsible for the formation of esomeprazole

sulphone.[17] Mean AUC and C_{max} were increased by ≈100% and ≈60% in esomeprazole recipients who lacked functional CYP2C19 (i.e. poor metabolisers); no dosage adjustment is recommended in such patients.[7]

- In healthy volunteers, 77.0 and 18.5% of a single oral dose of esomeprazole 40mg was recovered in urine and faeces; <1% of the parent compound was found in the urine.[16]
- On days 1 and 5, the mean systemic clearance of intravenous esomeprazole 20 mg/day was 17.1 and 11.3 L/h and the mean elimination half-life was 0.79 and 1.05 hours.[8]

Special Patient Populations

- The use of esomeprazole in special patient populations has been reviewed previously.[5,6] Briefly, compared with patients with GORD and normal hepatic function, the pharmacokinetics of oral esomeprazole were largely unaltered in patients with mild to moderate hepatic impairment, although plasma esomeprazole levels were increased in patients with severe hepatic impairment (section 5).[18]
- No clinically significant changes in the pharmacokinetics of oral esomeprazole occurred in the elderly and dosage adjustment is not needed in this population.[19] The metabolism of esomeprazole is not expected to be altered in patients with renal dysfunction, although caution is recommended in patients with severe renal impairment.[7] No differences between men and women in esomeprazole pharmacokinetics were seen with repeat administration and dosage adjustment is not needed. [7]

Potential Drug Interactions

- Esomeprazole has low potential for interaction with other drugs.[20] Clarithromycin (an inhibitor of CYP3A4) increased the AUC of esomeprazole ≈2-fold, although this was not thought likely to be of clinical significance.[20]
- Studies with the CYP2C19 substrates diazepam, phenytoin and (*R*)-warfarin showed that esomeprazole has the potential to inhibit CYP2C19.[20] Although the minor effects seen were not considered to be of clinical relevance,[20] the dosage of CYP2C19 substrates may need to be reduced.[7] Moreover, in patients receiving phenytoin or warfarin, plasma phenytoin concentrations and the international normalised ratio should be monitored when esomeprazole therapy is started or withdrawn.[7]

3. Therapeutic Efficacy

The efficacy of intravenous esomeprazole in patients with erosive oesophagitis was examined in a randomised multicentre study.[21] Patients were aged ≥18 years and had endoscopically-confirmed erosive oesophagitis (Los Angeles grade A–D). Across the treatment groups, 31.4–39.5% of patients had grade A oesophagitis, 38.3–45.6% had grade B, 19.8–22.1% had grade C and 1.3–3.5% had grade D.

Patients received double-blind treatment for 1 week with esomeprazole 40mg administered once daily as an intravenous injection over 3 minutes (n = 79), an intravenous infusion over 30 minutes (n = 81) or orally (n = 86).[21] All patients then received oral esomeprazole 40mg once daily for 3 weeks.

The main efficacy outcome was healing (assessed endoscopically and defined as no mucosal breaks).[21] Efficacy was assessed using intent-to-treat analysis. This study is available as an abstract and poster.

- In patients with erosive oesophagitis, there were no significant differences in healing rates between recipients of intravenous (injection or infusion) and oral esomeprazole.[21] After 4 weeks' therapy, the healing rate was 79.7% (95% CI 69.2, 88.0%) in patients receiving esomeprazole by intravenous injection, 80.2% (95% CI 69.9, 88.3%) in patients receiving esomeprazole by intravenous infusion and 82.6% (95% CI 72.9, 89.9%) in patients receiving oral esomeprazole.[21]

4. Tolerability

The tolerability of intravenous esomeprazole was assessed in the well designed study discussed in section 3.[21] Patients with erosive oesophagitis received esomeprazole 40mg once daily by intravenous injection (n = 79) or infusion (n = 81) or orally

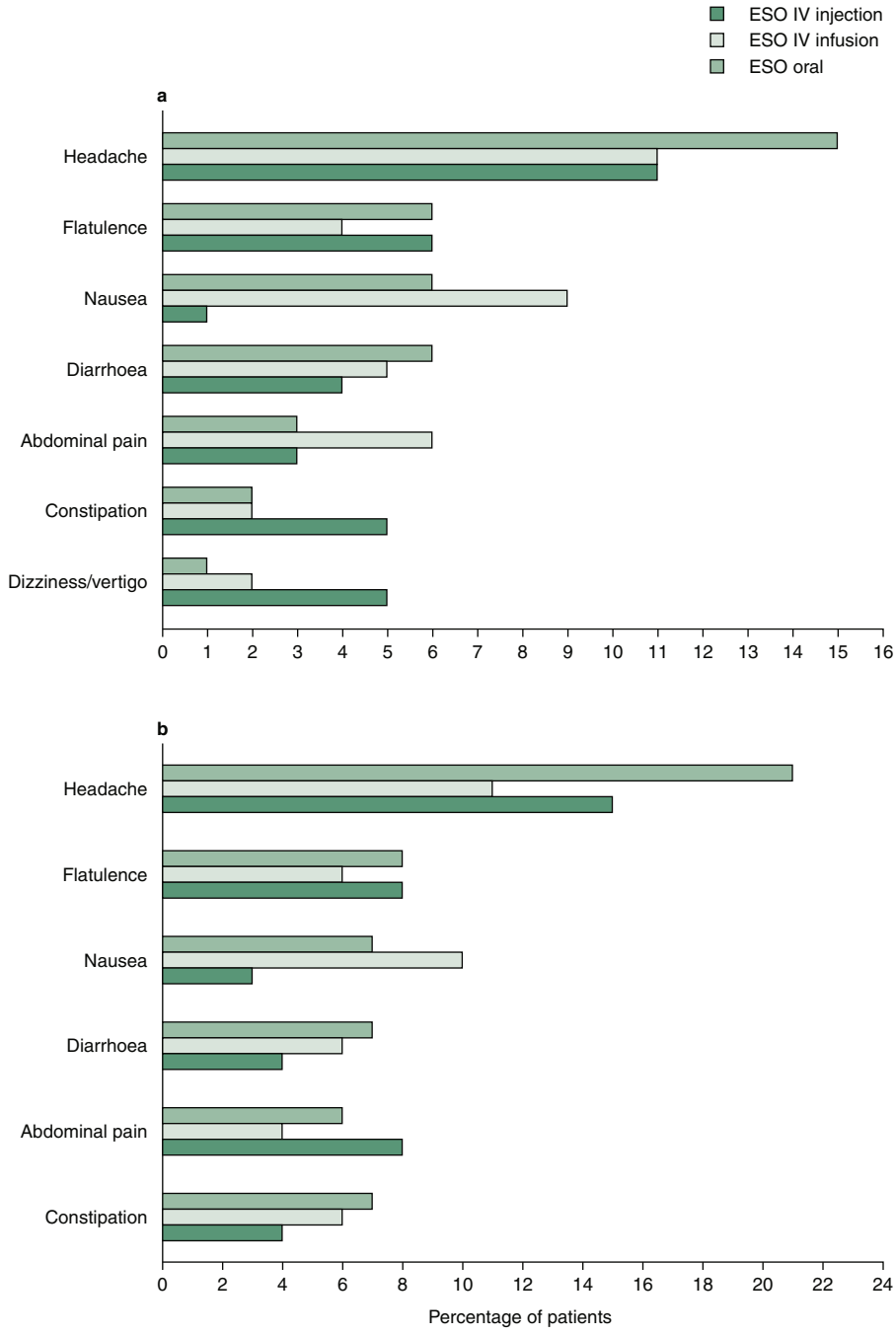

Fig. 3. Adverse events in patients receiving intravenous (IV) or oral esomeprazole (ESO). In this randomised, multicentre study, patients with erosive oesophagitis received ESO 40mg once daily by IV injection (n = 79), IV infusion (n = 81) or orally (n = 86) for 1 week in a double-blind manner; all patients received oral ESO 40mg once daily for the next 3 weeks. Adverse events were reported after (**a**) 1 and (**b**) 4 weeks' treatment.[21]

(n = 86) for 1 week, followed by oral therapy for the next 3 weeks. Statistical analyses were not reported.

- Intravenous esomeprazole (administered by infusion or injection) was generally well tolerated in patients with erosive oesophagitis.[21] The type and incidence of adverse events was similar in recipients of esomeprazole administered intravenously or orally (figure 3).
- After 1 week's therapy, adverse events were reported in 56 and 63% of patients who received esomeprazole by intravenous injection or infusion and in 60% of patients who received oral esomeprazole.[21] Serious adverse events were reported in oral esomeprazole recipients at 1 (n = 1) and 4 weeks (n = 4), but not in recipients of intravenous esomeprazole.
- The most commonly reported adverse events (≥5% in any group) included headache, flatulence, nausea, diarrhoea, abdominal pain, constipation and dizziness/vertigo (figure 3).[21]
- No clinically relevant changes in laboratory values, ECG findings, vital signs, physical examination findings or visual fields occurred during the study.[21]

5. Dosage and Administration

Intravenous esomeprazole may be administered by infusion (over 10–30 minutes) or injection (over ≈3 minutes [20 mg/day] or ≥3 minutes [40 mg/day]).[7] A dosage of 40mg once daily is recommended for the treatment of reflux oesophagitis and a dosage of 20mg once daily is recommended for the symptomatic treatment of GORD.[7] Intravenous esomeprazole is intended for short-term use and patients should be switched to oral esomeprazole as soon as possible.[7]

The esomeprazole dosage should not exceed 20 mg/day in patients with severe hepatic impairment (section 2).[7] Esomeprazole should not be administered to children; no data are available in this patient population.[7]

6. Intravenous Esomeprazole: Current Status

Intravenous esomeprazole is approved in the EU as an alternative to oral treatment in patients with GORD for whom oral therapy is not appropriate. Specifically, it is approved for the treatment of reflux oesophagitis and/or severe reflux symptoms. Intravenous esomeprazole had similar antisecretory activity to oral esomeprazole and achieved better gastric acid control than intravenous pantoprazole or omeprazole. Intravenous esomeprazole achieved a 4-week healing rate of ≈80% in patients with erosive oesophagitis and was generally well tolerated, with a tolerability profile similar to that of oral esomeprazole.

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