AWMSG Secretariat Assessment Report – Advice no. 0712
Esomeprazole (Nexium® IV) 40 mg powder for solution for injection/infusion

This assessment report is based on evidence from a limited submission by AstraZeneca UK Ltd on 18 November 2011[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Esomeprazole (Nexium® IV) is indicated, in children and adolescents aged 1–18 years, for gastric antisecretory treatment when the oral route is not possible, such as gastro-oesophageal reflux disease in patients with erosive reflux oesophagitis and/or severe symptoms of reflux[2].
Dosing	Paediatric patients who cannot take oral medication may be treated parenterally once daily, as a part of a full treatment period for gastro-oesophageal reflux disease. Usually the intravenous treatment duration should be short and transfer to oral treatment should be made as soon as possible. The paediatric dose is 10-40 mg depending on age, weight and indication, administered intravenously once daily as an injection over a period of at least 3 minutes or an infusion over 10-30 minutes. Please refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	18 July 2011[1,2] (licensed for use in adults on 10 March 2005[2]).

2.0 DECISION CONTEXT

2.1 Background

Gastro-oesophageal reflux (GOR) is the passage of gastric contents into the oesophagus and is a normal physiological process that occurs several times daily in healthy infants, children and adults[3,4]. Sensations of heartburn and acid regurgitation, two symptoms of GOR, are reported to occur on a weekly basis in approximately 2% of 3–9-year old children and 5–8% of 10–17-year old children[5]. GOR disease (GORD) occurs when the reflux of gastric contents causes troublesome symptoms or complications, such as erosive oesophagitis[3,4]. North American data suggests the incidence of GORD in paediatric patients is approximately 1%[6]. Based on company-sought Welsh expert opinion the company submission provides an estimate of 50 patients a year where intravenous (IV) treatments would be administered due to severe GORD in patients aged 1–18 years [1].

Paediatric patients with GORD commonly receive antacids, histamine-2 receptor antagonists or proton pump inhibitors (PPIs) as initial therapy[7]. PPIs such as omeprazole and esomeprazole inhibit the gastric proton pump (H^+K^+-ATPase), thereby preventing acid secretion by the gastric parietal cells. The oral formulation of esomeprazole is licensed for use in paediatric patients for the treatment of erosive reflux oesophagitis and long-term management to prevent relapse; symptomatic

treatment of GORD; and in combination with antibiotics for the treatment of duodenal ulcer caused by *Helicobacter pylori* (see relevant SPCs for more information regarding specific indications)[8–10]. The licence extension considered in this submission is for the use of the IV formulation in children and adolescents aged 1–18 years, for gastric antisecretory treatment when the oral route is not possible[1,2].

2.2 Comparators

The comparator requested by the Welsh Medicines Partnership (WMP) was omeprazole IV. The omeprazole IV SPC states that there is limited experience of use in paediatric patients[11]; however the British National Formulary for Children (BNF-C) provides recommended doses for children ≥ 1 month old[12].

2.3 Guidance and related advice

- NHS Evidence. Clinical Knowledge Summaries: gastro-oesophageal reflux disease in children younger than 2 years of age (2011)[13].
- North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). Pediatric gastroesophageal reflux clinical practice guidelines (2009)[3].
- National Institute for Health and Clinical Excellence (NICE). Clinical Guideline 17. Dyspepsia: Managing dyspepsia in adults in primary care (2004)[14]

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

As part of the submission, the company has provided analyses of the pharmacokinetic profiles of the IV formulations of esomeprazole and omeprazole in paediatric patients[1]. Esomeprazole is the s-isomer of omeprazole and has similar pharmacodynamic activity[2]. The single IV pharmacokinetics study described in Section 3.1 was used to bridge to existing oral paediatric pharmacokinetic, safety and efficacy data of esomeprazole.

The submission also includes a comparison of use of the oral formulations of esomeprazole and omeprazole in adult patients for the management of symptoms of GORD or oesophagitis[1]. As current NICE guidance for the treatment of dyspepsia states that there is no evidence that any one PPI is more effective than another at equivalent doses[14], this analysis is not discussed further.

3.1 Esomeprazole IV use in paediatric patients

The multicentre, open-label, pharmacokinetics study D9615C00021 evaluated the use of an IV injection of esomeprazole administered once daily for four days in hospitalised patients aged 0–17 years that had been considered for acid suppression therapy. Patients ≥ 6 years were randomised to receive one of two doses dependent on age; patients 0–5 years received doses based on weight and/or age (See Table 1 for more details)[15,16]. Doses used were based on previous adult and paediatric studies using oral esomeprazole[1]. Blood samples (≤ 8) were taken from patients before and after (5 minutes to 8.5 hours) each dose[15,16]. The primary endpoint was the area under the plasma concentration versus time curve (AUC_T) on day 4 of the study; secondary endpoints included other pharmacokinetic measures, such as maximum steady-state plasma concentration ($C_{ss,max}$), steady-state volume of distribution (V_{ss}) and total plasma clearance (CL) [15–17].

An overview of endpoint results is presented in Table 1. The AUC_T for esomeprazole ranged between 2.9 and 42 micromol·h/L in the studied population, whilst $C_{ss,max}$ ranged between 2.73 micromol/L and 29.4 micromol/L[1,15,16]. There was a proportional increase in the AUC_T when the dose of esomeprazole was doubled in patients aged ≥ 6 years[15,16]. The company submission notes that the results are reported to be consistent with previous results obtained for oral esomeprazole in children and adults[1].

Table 1. Overview of endpoint results from study D9615C00021[15,16].

Age	Dose	Number of patients	AUC_T (micromol·h/L) Mean (Range)	$C_{ss,max}$ (micromol/L) Mean (Range)	CL (L/h) Mean (Range)	V_{ss} (L) Mean (Range)
0–1 month	0.5 mg/kg	6	7.5 (4.5–20.5)	3.71 (2.73–5.77)	0.5 (0.1–1.0)	1.1 (0.8–2.2)
1–11 months	1 mg/kg	6	10.5 (4.5–22.2)	8.68 (4.51–14.0)	1.7 (0.9–3.1)	1.6 (1.5–1.7)
1–5 years	10 mg	7	7.9 (2.9–16.6)	9.37 (4.40–17.2)	3.4 (1.6–9.5)	3.3 (2.4–4.6)
6–11 years	10 mg	8	6.9 (3.5–10.9)	5.60 (3.13–13.2)	3.8 (2.7–5.1)	6.7 (4.0–14.0)
	20 mg	8	14.4 (7.2–42.3)	8.83 (3.36–29.4)	3.6 (1.1–8.0)	6.8 (4.9–10.7)
12–17 years	20 mg	6	8.1 (4.7–15.9)	7.10 (4.76–9.02)	7.0 (3.4–12.3)	9.5 (7.8–11.3)
	40 mg	8	17.6 (13.1–19.8)	10.5 (7.82–14.2)	6.4 (5.5–8.7)	10.9 (8.0–15.9)

AUC_T: area under the plasma concentration time curve, $C_{ss,max}$: maximum steady-state plasma concentration, V_{ss}: steady-state volume of distribution, CL: total plasma clearance.

The company submission highlighted a Food and Drug Administration review of esomeprazole use in paediatric patients[1]. This demonstrated that although lower doses of esomeprazole IV are administered than during the oral dosing regimen, exposures are higher and more consistent across dose groups[18]. Oral use of esomeprazole has previously been found to be efficacious in the treatment of symptoms and improvement of quality of life in paediatric patients with GORD[19–21].

3.2 Omeprazole IV use in paediatric patients

The omeprazole IV SPC notes that there is limited experience of omeprazole IV in paediatric patients[11]. However, it has been demonstrated that the pharmacokinetics of oral and IV omeprazole in paediatric patients are similar to those reported in adults[22,23]. Oral use of omeprazole has also been reported to improve symptoms in paediatric patients with GORD or oesophagitis[24–26].

3.3 Comparative safety of esomeprazole IV in paediatric patients

The company submission states that the adverse events (AEs) reported were consistent with the known safety profile of esomeprazole and the natural history of health and disease-related events in a paediatric population that is predominantly from hospital intensive care units. It also notes that no new safety signals were identified in paediatric patients treated with esomeprazole IV and no safety concerns were raised based on reported AEs[1].

In study D9615C00021, one or more AEs were reported by 31 patients (54.4%, n = 57), of which the most common were constipation (10.5%) and pyrexia (8.8%); AEs considered related to esomeprazole treatment were reported as mild to moderate in intensity in three patients (5.3%). Eight non-fatal, serious AEs were reported in six

patients (10.5%). Two patients (3.5%) discontinued due to the following AEs: infusion-site extravasation, pneumonia and acute respiratory failure[27].

3.4 WMP critique

- An analysis of the clinical effectiveness of the IV formulation of esomeprazole for gastric antisecretory treatment in paediatric patients has not been provided; in addition, the submission does not include a comparison with omeprazole. The company submission included studies demonstrating that the pharmacokinetic properties of these therapies are similar to those observed following treatment with the oral formulation[1]. This approach was based upon guidance produced by the European Medicines Agency[28], which states that extrapolation from efficacy data in adult patients may be appropriate where a medicinal product is to be used in paediatric patients for the same indication as that approved in adults, where the disease process is similar and the outcome likely to be comparable between populations. The guidance suggests that pharmacokinetic and safety studies in paediatric patients likely to receive the therapy may provide adequate information for use by allowing the selection of doses that will produce blood levels similar to those observed in adults[28].
- It should be noted that placebo-controlled trials demonstrating the efficacy of PPIs for the treatment of GORD symptoms in the paediatric population are lacking[3,6]. Additionally, the company submission provides evidence of the pharmacokinetics and safety of esomeprazole which is based upon abstracts from conference proceedings and has not undergone peer review[1,15,16,27].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

Cost-effectiveness evidence is not required for a limited submission.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company submission contains a simple estimation of budgetary impact associated with the use of esomeprazole IV compared to omeprazole IV (unlicensed in this patient population) as requested by WMP[1]. Using Welsh population statistics, the company estimated that there are currently 580,000 children and adolescents aged 1–18 years in Wales. Using prevalence estimates for GOR in 3- to 17-year-old children in the USA[5], the company estimated that there are currently 23,000 (4%) children and adolescents with GORD in Wales. Based on company-sought Welsh expert opinion, the company anticipates approximately 50 patients per year will be eligible for esomeprazole IV where the oral route is not possible due to severe GORD. Assuming all 50 patients are treated with esomeprazole IV for ten days, the company estimates an annual cost of £1,565. Compared with £2,705 if omeprazole IV were used, this would be equivalent to a cost saving of £1,140 per year.

5.1.2 WMP critique

Esomeprazole IV and omeprazole IV are assumed to be therapeutically equivalent in the paediatric population, based on pharmacokinetic data and extrapolation of efficacy data from the adult population taking oral formulations. There are no comparative effectiveness data available in the paediatric population. There are few data with which to estimate patient numbers in Wales. Estimates of GORD prevalence in children aged

1–18 years in Wales are extrapolated from a study of parent-reported symptoms of GOR in children in the USA[5]; however, the number of patients eligible for treatment with esomeprazole IV is based on company-sought expert opinion. Therefore, the estimated number of children who may be treated with esomeprazole IV or omeprazole IV in Wales is subject to uncertainty.

A ten-day treatment period is assumed and no alternative scenario analyses have been presented to address the uncertainty associated with the number of eligible patients or the duration of treatment. The company has not included the costs of 0.9% sodium chloride solution required for reconstitution of esomeprazole IV if given by injection (the omeprazole IV injection pack contains the solvent, which is included in the list price). Both esomeprazole IV and omeprazole IV attract additional costs of diluents when administered via infusion. The stated cost savings are therefore likely to be marginally overestimated. Despite this, the acquisition cost of esomeprazole IV remains lower than that of omeprazole IV (see Table 2 below), irrespective of treatment duration and patient numbers.

5.2 Comparative unit costs

Esomeprazole is the only PPI licensed for use in the paediatric population; however omeprazole IV is reported to be used off-label. Table 2 shows the examples of daily acquisition costs in this patient population.

Table 2. Example acquisition costs for esomeprazole IV and omeprazole IV.

Drug	Regimen	Cost per patient per day
Esomeprazole (Nexium®) IV 40 mg powder for reconstitution	< 20 kg: 10 mg once daily 1–11 years and ≥ 20 kg: 10–20 mg once daily	£3.13*
(Plus sodium chloride 0.9% for IV use 5 ml vial if given by injection)	12–18 years, 40 mg once daily	(+£0.32)
Omeprazole IV 40 mg powder and solvent for injection (Losec®) (Unlicensed in this population)	Doses up to 40 mg once daily assumed	£5.41*
*Costs are based on MIMS[29] and British National Formulary[30] list prices for injection. If administered via infusion both PPI acquisition costs attract additional costs of up to 100 ml diluent. Administration of lower doses (10–20 mg once daily) requires disposal of the remainder of the 40 mg vial. See the relevant SPCs[2,11] for dose, reconstitution and storage details. This table does not imply therapeutic equivalence of drugs or the stated doses.		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

WMP is of the opinion that esomeprazole IV is suitable for specialist only prescribing within NHS Wales.

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