esomeprazole, 40mg vial of powder for solution for intravenous injection or infusion (Nexium I.V.®) No. (578/09)
AstraZeneca

09 October 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

esomeprazole (Nexium I.V.®) is accepted for use within NHS Scotland for prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

In patients with high-risk peptic ulcer bleeding, high-dose intravenous esomeprazole significantly reduced recurrent bleeding at 72 hours compared to placebo.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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

Dosing information

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

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

Product availability date

29 April 2009.

Summary of evidence on comparative efficacy

Esomeprazole is the S-isomer of omeprazole. It is a specific inhibitor of the enzyme H^+K^+-ATPase, the acid pump in the parietal cell, and inhibits both basal and stimulated acid secretion.

Peptic ulcer bleeding (PUB) is a serious and potentially life threatening condition. To achieve haemostasis patients receive endoscopic therapy to active arterial bleeding, non-bleeding visible vessels or an adherent blood clot. The aim of additional acid suppression therapy is to maintain intragastric pH >6 to stabilise clots and prevent rebleeding. Patients who rebleed after endoscopic therapy have increased mortality and require urgent intervention.

Efficacy of iv esomeprazole was determined from one double-blind, parallel group, placebo-controlled, multicentre study. Patients were ≥18 years and had undergone successful endoscopic haemostatic treatment (EHT) of a bleeding gastric or duodenal ulcer using injection therapy with adrenaline and/or thermal coagulation or application of hemoclips. Patients were required to have only one bleeding gastric or duodenal ulcer that was at least 5mm in diameter and showed one of the following endoscopic stigmata of recent haemorrhage: arterial bleeding (Forrest class Ia), oozing (Forrest class Ib), non-bleeding visible vessel (Forrest class IIa), or adherent clot (Forrest class IIb). In the case of Forrest Class IIb ulcers, after attempts to remove the clot by water irrigation or a cold snare, ulcers were either reclassified for inclusion as Forrest class Ia, Ib, or IIa or, if unsuccessful, included as Forrest class IIb. In addition, patients had an American Society of Anesthesiologists (ASA) score of 3 or less.

Of the 1,313 patients enrolled, 767 were randomised in a 1:1 ratio to esomeprazole 80mg bolus given iv over 30 minutes followed by an 8mg/hour infusion for 71.5 hours (n=376) or to placebo (n=391). One patient allocated to receive esomeprazole and two patients allocated to receive placebo were excluded from the intention to treat (ITT) analysis either because no medication was taken or there was no written informed consent. After iv infusion, both groups received oral esomeprazole 40mg per day for 27 days. Patients were mainly Caucasian (87%, Asian 7.1%), with a duodenal ulcer (59%, gastric 41%), Forrest class Ib and IIa (80% in each group) and an ASA score of 1 (39%) or 2 (48%). *H. pylori* was detected (positive or trace) in 68% of patients.

The primary endpoint was the rate of clinically significant recurrent peptic ulcer bleeding within 72 hours of endoscopic treatment. Clinically significant recurrent bleeding was defined by haematemesis with vomiting of >200mL of fresh blood or at least two of the following clinical findings; vomiting of fresh blood, fresh blood in the nasogastric tube, haematochezia or melaena after a normal stool, a decrease in haemoglobin >20g/L (or decrease in haematocrit >6%) or an increase in haemoglobin <10g/L (or increase in haematocrit <3%) during 24 hours despite 2 or more units of blood transfused during 24 hours; or unstable vital signs with systolic blood pressure of ≤90mmHg or pulse of ≥100 beats/minute (after having achieved haemodynamic stability). From the intention to treat analysis, significantly fewer patients receiving esomeprazole (5.9%, 22/375) than receiving placebo (10.3%, 40/389) had recurrent bleeding within the first 72 hours of treatment (absolute risk reduction of 4.4% [95% Confidence Interval (CI): 0.6% to 8.3%]). The difference in bleeding recurrence remained statistically significant at 7 days and 30 days. Esomeprazole also significantly reduced endoscopic retreatment, the number of blood units transfused within 72 hours and 30 days and the number of days hospitalised due to rebleeding compared with placebo within the 30 days treatment period.

Summary of evidence on comparative safety

During the 72 hour treatment phase, high dose iv esomeprazole was generally well tolerated. Gastrointestinal disorders were the most common adverse events in both treatment groups, mostly related to recurrent bleeding (esomeprazole 12% versus placebo 20%). Infusion-site reactions were reported in a higher proportion of esomeprazole treated patients compared with placebo (4.3% versus 0.5%) but these were of mild intensity, transient and did not lead to treatment discontinuation. Vascular disorders (phlebitis) also occurred more frequently in the esomeprazole group than in the placebo group (2.4% versus 0.5%). The rates of adverse events (esomeprazole 39% versus placebo 42%) and treatment discontinuations (esomeprazole 8.3% versus placebo 10%) were comparable for the two groups and only one death (in the esomeprazole group) occurred. During the 30 day study, three patients from the esomeprazole group died compared to eight patients from the placebo group; the difference between the groups was not significant.

Summary of clinical effectiveness issues

Intravenous esomeprazole is the only proton pump inhibitor (PPI) that is licensed in the UK for the prevention of rebleeding following therapeutic endoscopy for acute gastric or duodenal ulcers.

In the pivotal study endoscopic therapy was not standardised; some patients received adrenaline, thermal coagulation or hemoclips alone, whilst others received combination therapy, with about half receiving single therapy in each group. Scottish Intercollegiate Guidelines Network (SIGN) guidelines state that combinations of endoscopic therapy comprising an injection of at least 13ml of 1:10,000 adrenaline coupled with either a thermal or mechanical treatment are recommended in preference to single modalities. This recommendation was based on two meta-analyses which showed substantial reduction in bleeding rates following combination versus single endoscopy therapy. However, a post-hoc analysis of the pivotal study showed that the reduction in recurrent bleeding between esomeprazole and placebo groups was similar following single or dual endoscopic treatment.

Although no significant difference in mortality was observed between the esomeprazole and placebo groups at 72 hours or 30 days in the pivotal study, SIGN notes that a mortality benefit has been shown in high-risk patients (active bleeding or non bleeding visible vessel)

who have received high-dose PPI treatment (omeprazole 80mg bolus injection followed by 8mg/hour iv infusion for 72 hours) following endoscopy.

There is no comparative evidence for iv esomeprazole against the other PPIs that may be given intravenously, pantoprazole and omeprazole, currently being used outwith their marketing authorisation for the indication under review. However, based on the results of a mixed treatment comparison (pivotal study and five other studies) it is reasonable to assume that there is little to distinguish between iv esomeprazole and the other PPIs and that all three PPIs performed better than placebo. There were some differences between the studies; one study had an open-label design, two studies lacked discrete outcome variables, and three studies were carried out in Asian patients who have a greater treatment effect, so the findings may not be generalisable to Scottish patients. In all the studies there were differences in endoscopic therapy with some patients receiving endoscopic therapy only for spurting ulcer bleeding and others receiving endoscopic therapy for active bleeding or stigmata of recent haemorrhage (a non-bleeding visible vessel).

Esomeprazole powder for solution is licensed for use as an injection or infusion, unlike one of the comparator products where the injection and infusion are not interchangeable.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing high-dose esomeprazole with the two other intravenous PPIs (omeprazole and pantoprazole) in the prevention of rebleeding following therapeutic endoscopy in patients at high risk of rebleed. A decision tree model was used to estimate the costs and benefits of esomeprazole treatment over a 30-day time horizon. In the model, after 3 days of iv PPI treatment, patients had a risk of rebleed and following rebleed they had a risk of repeat EHT or surgery. Clinical data inputs for the economic model were estimated based on a mixed treatment comparison (MTC) of the three PPIs vs placebo based on rebleeding, repeat EHT and surgical intervention rates. Utility decrements associated with bleed and surgery were taken from a literature study and resource use was estimated based on the rates of surgery and EHT from the MTC. The manufacturer estimated that compared with omeprazole, esomeprazole would be less expensive (£32) and less effective (0.00015 QALY loss). Compared with pantoprazole, esomeprazole would be less expensive (£37) and less effective (0.00001 QALY loss).

Some weaknesses were noted with the economic analysis:

- A meta-analysis of the other PPIs showed that there is evidence of reduced mortality compared with placebo. No significant difference in mortality compared with placebo was observed in the esomeprazole pivotal study. However, the study would not have been powered to detect a difference and the meta-analysis of the other PPIs was only able to show a difference by pooling the results of four trials.
- The MTC showed that PPIs are more effective than placebo in terms of rebleeds, repeat EHT and surgery rates, but it does not show any difference between the treatments. As such, it may be more appropriate to assume no real difference between treatments in the model. This would result in esomeprazole being preferred on cost-minimisation grounds.
- The utility decrement for rebleed and surgery is quite small (0.01) compared with some values used in the literature. For example, a health technology assessment of PPIs in upper GI bleeding used utility values of 0.45 for the period of time in hospital after a rebleed and 0.78 for patients recovering at home. Additional sensitivity analysis using utility decrements of 0.1 and 0.2 showed that esomeprazole was still cost-effective.

There were some weaknesses with the economic model, but the three intravenous PPIs have broadly similar efficacy and esomeprazole has the lowest acquisition cost. As such, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN); Guideline number 105. Management of acute upper and lower gastrointestinal bleeding, published September 2008. SIGN states that high-dose iv proton pump inhibitor therapy (e.g. omeprazole or pantoprazole 80mg bolus followed by 8mg/hour infusion for 72 hours) should be used in patients with major peptic ulcer bleeding (active bleeding or non-bleeding visible vessel) following endoscopic haemostatic therapy. This guideline predates the licensed indication of iv esomeprazole that is under review in this submission.

Additional information: comparators

There are no licensed comparators. Omeprazole and pantoprazole are used outwith their licensed indications.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
Esomeprazole	**80mg iv bolus followed by 8 mg/hour iv infusion for 72 hours**	**53**
*Omeprazole	80mg iv bolus followed by 8 mg/hour iv infusion for 72 hours	92
Pantoprazole	80mg iv bolus followed by 8 mg/hour iv infusion for 72 hours	87

Doses are for general comparison and do not imply therapeutic equivalence. Costs for omeprazole and pantoprazole from eVadis on 4 August 2009 and cost for esomeprazole from applicant on 6 August 2009. Cost per course calculated based on use of full vials. Dose regimen for omeprazole and pantoprazole from SIGN guideline number 105. *Omeprazole injection and infusion are not interchangeable.

Additional information: budget impact

The number of patients at high risk of rebleeding was estimated to be 299 in year 1 and 280 in year 5. The manufacturer estimated the gross drug budget impact of iv esomeprazole at £16k in year 1 and £15k in year 5. The manufacturer estimated the net budget impact of esomeprazole would be savings of between £10k and £12k in year 1 and between £9k and £11k in year 5, based on the drug budget only. The budget impact estimates are based on an assumed 100% market share.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 10 September 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted reference was supplied with the submission.

A. Sung JJ, Barkun A, Kuipers EJ et al. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding. Ann Intern Med. 2009;150:455-464