esomeprazole, 20mg and 40mg tablets (Nexium®) No. (422/07)
AstraZeneca UK Ltd

09 November 2007

The Scottish Medicines Consortium 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®) is accepted for use within NHS Scotland for the treatment of Zollinger-Ellison Syndrome.

Other proton pump inhibitors are available for this indication at a lower cost per treatment period.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of Zollinger-Ellison Syndrome.

Dosing information

Initially 40mg twice daily, then individually adjusted and treatment continued for as long as clinically indicated. The majority of patients can be controlled on doses between 80mg and 160mg daily. With doses above 80mg daily, the dose should be divided and given twice-daily.

Product availability date

2 May 2007

Summary of evidence on comparative efficacy

Esomeprazole, the S-isomer of omeprazole, is a proton pump inhibitor (PPI) that inhibits the acid pump in parietal cells, thereby reducing gastric acid secretion.

Zollinger-Ellison Syndrome (ZES) is a rare but potentially life-threatening condition that is characterised by refractory peptic ulcer disease, diarrhoea and severe gastric acid hypersecretion associated with an islet-cell tumour of the pancreas (gastrinoma). Effective gastric acid control is essential in its management.

Evidence came from one phase III, open label, 12-month trial which recruited 21 patients, over the age of 18, with basal acid hypersecretion associated with ZES (including sporadic or multiple endocrine neoplasia-1), which accounted for 19 patients, or idiopathic gastric acid hypersecretion (IH). The trial was uncontrolled because use of placebo was considered unethical in this patient group and use of an active control is not standard practice in ZES studies due to difficulties in achieving the required sample size. The primary objective was to determine if esomeprazole, in appropriately titrated doses, controlled gastric acid hypersecretion in these patients at month 12. The measured parameter was basal acid output (BAO). Patients were diagnosed with hypersecretion if levels were at least 15 mmol/h (10 mmol/h if they had had previous gastric acid reducing surgery) and were considered to be controlled if levels were <10 mmol/h (or <5 mmol/h if previous surgery).

The study consisted of an acid control phase followed by an acid maintenance phase. During the control phase, patients were switched from their previous PPI to esomeprazole 40mg twice daily (bd), or 80mg bd for 2 patients, and titrated to 80mg bd or 120mg bd as needed, or to an alternative dosage (as allowed by consultation with the company). BAO was measured on day 1 (baseline) and day 10. Once control was achieved, patients entered the maintenance phase, where doses could again be altered within the previously mentioned regimens. This phase involved taking BAO measurements at months 3, 6 and 12. An antacid preparation was allowed for symptom breakthrough throughout and parenteral PPIs or H_2-receptor antagonists could be used in an emergency.

The intention-to-treat (ITT) population (n=21) included all patients who received at least one dose of study medication and had at least one valid BAO measurement.

Gastric acid secretory rates were controlled with esomeprazole in 95% of patients (20/21) at month 6 and 90% (19/21) at month 12. Median BAO rates were 0.18mmol/h (range 0.00 to 5.9mmol/h) and 0.19mmol/h (range 0.00 to 35.3mmol/h) at months 6 and 12 respectively. The target gastric acid secretory control was achieved with esomeprazole 40mg bd in 67%

(14/21) of patients at month 12; 19% (4/21) required 80mg bd and 4.8% (1/21) required 80mg three times a day (tid). Gastric acid secretory rates were controlled effectively in 95% (20/21) of patients by day 10 and in 18/20 (90%) control was sustained for the remainder of the clinical study.

Summary of evidence on comparative safety

At daily doses of 80mg to 240mg, esomeprazole was generally well tolerated Most adverse events were mild to moderate in severity and resolved spontaneously, without dose reduction or drug cessation. One of 4 serious adverse events (hypomagnesemia) was considered possibly related to esomeprazole.

Summary of clinical effectiveness issues

Patient numbers in the supporting trial were small and there were no comparators, though this is not unexpected with this rare condition.

Doses could not be titrated below a set minimum (80mg), so it is not known if any patients could have been controlled on a lower dose (note that most patients were controlled on the lowest dose).

Long-term safety data relating to high doses of esomeprazole are lacking.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis of esomeprazole compared to rabeprazole as the primary comparator for the treatment of ZES/IH, and a secondary analysis comparing esomeprazole to other PPIs licensed for ZES. The specific target population described was patients who are particularly vulnerable to relapse (i.e. those who have undergone gastric acid reducing surgery or those with severe oesophagitis) or who are unresponsive to their current PPI therapy. The rationale for the choice of rabeprazole as primary comparator was its previous SMC approval for use in ZES (after an abbreviated submission in January 2006) and an assumption that it is the PPI most likely to be displaced by esomeprazole. However, rabeprazole is unlikely to represent the appropriate or only possible comparator PPI for this target population.

Despite the small size and non-comparative design of the PPI trials in ZES/IH, an indirect comparison was performed that demonstrated the roughly equal effectiveness of each of the PPIs in gastric acid for ZES relative to esomeprazole. An analysis of annual drug cost found that esomeprazole resulted in net cost savings compared to rabeprazole, based on average dose used in respective clinical trials and therefore would be the preferred treatment on cost-minimisation grounds. In the secondary analysis it was more costly than generic lansoprazole, omeprazole, or pantoprazole. There was uncertainty in mean dosing derived from small clinical studies and in how representative this is of clinical practice in the target population. A dose range was tested in sensitivity analysis resulting in the possibility of a net cost being incurred for esomeprazole compared to rabeprazole.

An important weakness was that the studies for rabeprazole and esomeprazole included in the indirect comparison differed in patient population and so did not enable a comparison of efficacy appropriate for the target population. Whilst it is accepted that there are data limitations due to small patient populations, the trials for esomeprazole and rabeprazole had

the smallest patient numbers of the PPI trials in ZES increasing the difficulty to compare results. Also on the evidence presented, esomeprazole cannot be considered cost-effective for ZES/IH compared to the other PPIs, although again the data for comparisons are limited.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: previous SMC advice

After review of an abbreviated submission, the Scottish Medicines Consortium (SMC) issued advice in January 2006 that:

Rabeprazole (Pariet®)10mg and 20mg tablets is accepted for use within NHS Scotland for the treatment of Zollinger-Ellison syndrome. Other proton pump inhibitors are available for this indication at a lower cost per treatment period.

Additional information: comparators

All other PPIs are licensed for this indication and included for comparison.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£) Cost per course (£)
esomeprazole	**80 – 160mg daily ***	**655-1310**
rabeprazole	60 – 120mg daily	825 - 1650
pantoprazole	80 – 160mg daily	556 - 1113
lansoprazole	60 – 180mg daily	101 - 302
omeprazole	20 – 120mg daily	52 - 313

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on30th August 2007.

*Note that in the reported trial, the maximum dose used was 240mg. This would incur a cost of £1965. The dose range used above is that given in the Summary of Product Characteristics, from where the dose ranges for the comparators have been obtained.

Additional information: budget impact

The budget impact was estimated by the manufacturer as a direct cost for esomeprazole of £2k in 2008 for an estimated two Zollinger-Ellison syndrome patients treated, and £3k per annum thereafter for three patients per year. The budget impact is limited to the sub group of patients, estimated to represent 10%, who are vulnerable to relapse or unresponsive to current PPI therapy. Net savings of £200 to £300 per annum are estimated due to displacing the use of other medications for these patients.

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 11 October 2007.

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.

Metz D.C et al., Acid Output Control with Esomeprazole in Patients with Zollinger-Ellison Syndrome and Idiopathic Gastric Acid Hypersecretion: Final 12-month results. Gastroenterol 2006; 130 (4 Suppl 2): A 387 [abstract M1977]