Scottish Medicines Consortium

esomeprazole 20mg and 40mg tablets (Nexium®) No. (368/07)

AstraZeneca UK Ltd

Extension of current licence for the treatment of gastro-oesophageal reflux disease to include patients from 12 years of age

6 April 2007 *(Issued May 2007)*

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®) is accepted for restricted use within NHS Scotland, for patients in the age group 12-17 years inclusive, for the treatment of erosive reflux oesophagitis, the long-term management of patients with healed oesophagitis to prevent relapse, and the symptomatic treatment of gastro-oesophageal reflux disease.

The use of esomeprazole for this indication and age group should be restricted to patients in whom maximum licensed doses of generic proton pump inhibitors have been ineffective.

The pharmacokinetics of esomeprazole in adolescents have been shown to be similar to those seen in adults; there is no evidence of comparative efficacy in adolescents in this indication.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of erosive reflux oesophagitis; long-term management of patients with healed oesophagitis to prevent relapse; symptomatic treatment of gastro-oesophageal reflux disease in patients aged 12-17 years inclusive.

Dosing information

Treatment of erosive reflux oesophagitis: 40mg once daily for four weeks continued for an additional four weeks if the oesophagitis has not healed or if symptoms persist.

Long-term management of patients with healed oesophagitis to prevent relapse: 20mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease: 20mg once daily in patients without oesophagitis. If symptom control has not been achieved after four weeks, the patient should be further investigated.

Product availability date

April 2007

Summary of evidence on comparative efficacy

Gastro-oesophageal reflux disease (GORD) is the reflux of gastric contents into the oesophagus causing symptoms of heartburn and/or acid regurgitation that are sufficient to interfere with quality of life. Maintenance of intragastric acidity above the threshold of pH 4.0 has been claimed to reduce the intensity of GORD symptoms partly due to the absence of active pepsin. Esomeprazole is the S-isomer of omeprazole and suppresses gastric acid secretion by inhibition of the H^+ K^+ ATPase enzyme (proton pump) in parietal cells, thus blocking the final step in acid production.

Esomeprazole is licensed for the treatment of GORD in adults. There is no evidence on comparative efficacy for esomeprazole in the treatment of GORD in adolescents.

The pharmacokinetics of esomeprazole was investigated in a study of 28 adolescents aged 12-17 (mean 14.3) years who had a history of GORD symptoms of between seven months and five years. After repeated daily dosing with esomeprazole 20mg or 40mg, the total exposure (area under the plasma concentration time curve) and time to maximum plasma drug concentrations were comparable with previously reported adult values. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 17 years was similar to that observed in adult patients with GORD.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The adverse event profile of the patients (12 to 17 years) observed in the clinical programme was consistent with that of adults in previous esomeprazole clinical trials. Both 20mg and 40mg esomeprazole were well tolerated by these patients and no new safety concerns arose in this population. In the non-comparative safety study the most frequently reported treatment related adverse events in adolescents were headaches (12, 8.1%), abdominal pain (4, 2.7%), diarrhoea (3, 2.0%) and nausea (3, 2.0%).

Summary of clinical effectiveness issues

Unfortunately there are no comparative studies of esomeprazole with omeprazole, the other licensed therapy for the treatment of GORD in adolescents.

A systematic review of PPIs in reflux oesophagitis in adults found significantly lower healing rates for omeprazole 20mg, lansoprazole 30mg, pantoprazole 40mg and rabeprazole 20mg compared with esomeprazole 40mg.

Extrapolation of data from the trials and post-marketing experience of esomeprazole in the treatment of GORD in adults appears to be justified by the close resemblance of the clinical course and manifestation of the disease in adolescents and adults and the apparent similarity in the pharmacokinetics of esomeprazole in both populations.

Summary of comparative health economic evidence

The manufacturer presented a cost utility decision tree analysis of healing rates against non-healing rates for esomeprazole 40mg in moderate and severe GORD. Esomeprazole was evaluated against pantoprazole 40mg and rabeprazole 20mg, it being assumed that patients would already have tried and failed on lansoprazole and omeprazole.

Clinical effectiveness in terms of the relative risk of healing was drawn from a meta-analysis of adult patients taking “standard dose” PPIs or esomeprazole 40mg for reflux oesophagitis. The healing rate for pantoprazole and rabeprazole was assumed to be equal to that outlined in the omeprazole summary of product characteristics. The healing rate for esomeprazole was derived by applying the meta analysis relative risk of healing to this.

The duration of cure was estimated as being 180 days, this being inferred from pharmacy data which showed that adolescents receiving current PPIs typically receive them for around 80 days each year, but with each course only lasting around 37 days. The time between courses was assumed to be the duration of cure.

Quality of life data for moderate and severe GORD was taken from a time trade off survey among 1011 European GORD patients. Only the direct drug costs were included, on the basis of a common 56 day treatment for each of the three drugs. Esomeprazole was estimated to yield an additional 0.0017 QALYs over the 180 days of the cure for moderate GORD. This was at an additional cost of £7.76 relative to pantoprazole and £8.06 relative to rabeprazole. This yielded cost effectiveness estimates of £4,580 per QALY and £4,757 per QALY respectively.

In severe GORD the utility increment was estimated as 0.0024, with the same additional costs as above. This yielded cost effectiveness estimates of £3,271 per QALY relative to pantoprazole and £3,398 per QALY relative to rabeprazole.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

The PPI omeprazole and the histamine H_2 antagonists ranitidine and cimetidine are licensed for the treatment of GORD in the 12-17 years age group. Other PPIs have been used off label.

Additional information: costs

Doses are shown for general comparison and do <u>not</u> imply therapeutic equivalence.

	Product	**Regimen for treatment of erosive reflux oesophagitis**	**Cost per treatment course (£)**
Proton pump inhibitors	**esomeprazole (Nexium®)**	**40mg daily for 4-8 weeks**	**25.00 - 50.00**
	lansoprazole (non-proprietary)#	30mg daily for 4-8 weeks	5.55-11.10
	omeprazole (non-proprietary)	20mg daily for 4-8 weeks	4.45 - 8.90
Histamine H_2 antagonists	cimetidine (non-proprietary)	400mg four times daily for 4 - 8 weeks	5.28-10.57
	ranitidine (non-proprietary)	300mg daily for 4 -12 weeks	2.25-6.75

Costs accessed from eVadis on 29.1.07. # lansoprazole " off label" use

Additional information: budget impact

Based upon 25% of adolescent GORD patients failing on other proton pump inhibitors, the manufacturer estimates that around 370 would be eligible for esomeprazole in year 1 rising to 480 by year 5.

If all used esomeprazole this would have a direct gross drug cost of £27,831 in year 1 rising to £36,280 by year 5. The parallel figures for other proton pump inhibitors are approximately £4000 lower.

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 3 May 2007.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/

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 references were supplied with the submission.

Li J et al., Pharmacokinetic properties of esomeprazole in adolescent patients aged 12 to 17 years with symptoms of gastroesophageal reflux disease: a randomised, open-label study. Clinical Therapeutics 2006; 28 (3): 419-27

Edwards SJ et al. Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis – a comparison of esomeprazole with other PPIs. Aliment Pharmacol Ther 2006; 24: 743-750