Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

naproxen/esomeprazole 500mg/20mg modified release tablets (Vimovo®)
SMC No. (734/11)

AstraZeneca UK

07 October 2011

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

naproxen 500mg/esomeprazole 20mg (Vimovo®) is not recommended for use within NHS Scotland.

Indication under review: the symptomatic treatment of osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS), in patients who are at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient.

Studies have demonstrated that combined naproxen/esomeprazole was associated with a lower incidence of endoscopic gastric ulcers than NSAID alone and similar improvements in pain and functioning compared to a cyclo-oxygenase-2 selective inhibitor.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Symptomatic treatment of osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS), in patients who are at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient.

Dosing Information

One tablet to be swallowed whole twice daily, taken 30 minutes before food.

Product availability date

17 January 2011

Summary of evidence on comparative efficacy

This is a fixed dose, modified-release combination preparation of two established medicines; the NSAID naproxen 500mg enteric-coated (gastro-resistant) and the proton pump inhibitor (PPI) esomeprazole 20mg. The preparation provides a sequential delivery of esomeprazole and naproxen,with the instant release esomeprazole rapidly absorbed and the enteric-coated naproxen released shortly afterwards.

The submitting company has requested that SMC consider naproxen/esomeprazole when positioned for use in a sub-population of the licensed indication, namely for patients aged ≥65 years as increased age is an established risk factor for upper gastrointestinal adverse effects with NSAIDs.

Two identical, randomized, double-blind, multicentre, phase III studies compared naproxen/esomeprazole with naproxen alone in 434 and 420 patients with OA, RA, AS or other medical conditions expected to require ≥6 months NSAID therapy. Eligible patients were aged ≥50 years (or 18 to 49 years with a history of uncomplicated gastric or duodenal ulcer in the previous 5 years) and were *Helicobacter pylori* negative. Patients were randomised to receive naproxen/esomeprazole 500mg/20mg or naproxen 500mg twice daily for 6 months with stratification for use of aspirin (≤325mg daily). The primary endpoint was the cumulative incidence of endoscopic gastric ulcers. In both studies this was significantly lower in patients who received the naproxen/esomeprazole combination than in patients who received naproxen alone: 4.1% versus 23% in one study and 7.1% versus 24% in the other. Pooled analysis also demonstrated that the incidence of endoscopic gastric ulcers was significantly lower in naproxen/esomeprazole than naproxen patients in the subgroups of patients receiving aspirin (n=201) and not receiving aspirin (n=653). The incidence of duodenal ulcers was also significantly reduced in the naproxen/esomeprazole groups in both studies.

Two identical, randomised, double-blind, placebo-controlled, multicentre, phase III studies compared naproxen/esomeprazole with celecoxib in 614 and 610 patients aged ≥50 years with symptomatic knee OA. Patients were randomised to receive naproxen/esomeprazole 500mg/20mg twice daily, celecoxib 200mg daily or placebo for 12 weeks. These studies demonstrated the non-inferiority of naproxen/esomeprazole compared to celecoxib based on

three co-primary endpoints (mean change from baseline in Western Ontario and McMaster Osteoarthritis Index [WOMAC] pain, WOMAC function and patient global assessment [PGA] of OA).

Summary of evidence on comparative safety

Safety data from the four phase III studies described previously raised no new safety concerns.

A single-arm, open-label, phase III study assessed the long-term safety of naproxen/esomeprazole over 12 months. This enrolled 239 patients aged ≥50 years (or 18 to 49 years with a history of uncomplicated gastric or duodenal ulcer in the previous 5 years) with OA, RA or other condition requiring daily NSAID treatment to receive naproxen/esomeprazole 500mg/20mg twice daily for 12 months. The results identified no new safety issues, gastrointestinal or cardiovascular. Adverse events were reported in 73% of patients and these were treatment-related in 28%, lead to discontinuation in 19% and were serious in 5.4%. The most commonly reported adverse event was dyspepsia (7.9%).

Summary of clinical effectiveness issues

Long-term use of NSAIDs is associated with a marked risk of upper gastrointestinal adverse effects including gastric ulcers, perforations and bleeds. Treatment guidelines from SIGN and NICE recommend that patients receiving NSAIDs, particularly those with any upper gastrointestinal risk factors, should be co-prescribed a gastroprotective agent such as a PPI. This fixed dose combination of naproxen plus esomeprazole is licensed for use in patients who are at risk for developing NSAID-associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient. The submitting company has requested that SMC consider naproxen/esomeprazole in a sub-population of the licensed indication, namely those patients aged ≥65 years. Clinical efficacy data in this cohort are limited. Around one third of all patients included in the studies were ≥ 65 years but outcomes in this patient population were not reported separately.

The four phase III studies described demonstrated lower rates of endoscopic gastric ulcers with the naproxen/esomeprazole combination compared with naproxen alone and non-inferiority compared with celecoxib in terms of pain and functioning. However, there are no comparative data versus likely comparators in clinical practice (i.e. NSAID plus PPI prescribed separately).

The claimed advantage of this combination product is the guaranteed adherence to gastroprotection from the PPI each time the patient takes a dose of NSAID. The company suggests that this guaranteed adherence would be expected to lead to a reduction in NSAID-induced adverse gastrointestinal events, such as hospital admissions due to gastric ulcers. Although this is plausible, the clinical studies do not provide evidence to support this potential advantage.

The fixed dose combination requires patients to take a dose of esomeprazole 20mg twice daily, which is greater than the recommended dose for single-agent esomeprazole (20mg once daily) as a gastroprotectant. The potential advantages of guaranteed adherence to gastroprotection therefore needs to be balanced against the potential risks associated with patient exposure to a higher dose of PPI.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis comparing naproxen/esomeprazole with naproxen 1,000mg plus generic proton pump inhibitor (PPI), diclofenac 150mg plus PPI and ibuprofen 2,400mg plus PPI in patients with OA, RA and AS who are at risk for developing NSAID-associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or other NSAIDs is not considered sufficient. The generic PPI component of the comparator treatments was assumed to be a weighted average of omeprazole (65%) and lansoprazole (35%) to reflect current prescribing in Scotland. The focus of the submission was in line with the company's proposed positioning for the product i.e. in patients aged ≥65 years on the basis that increased age is a risk factor for NSAID-associated upper GI adverse events.

A lifetime Markov model was used based on the model developed by NICE for the osteoarthritis guideline. The main focus of the model was upper-GI and cardiovascular adverse events associated with long-term NSAID therapy on the assumption that naproxen/esomeprazole and the comparators were equally effective in terms of managing OA, RA and AS pain. As no comparative data were available, the adverse event rates were based on the data used in the NICE model with some adjustments made to account for dose, patient baseline risk, the addition of a PPI and the effect of sub-optimal adherence. The base case analysis assumed 73% adherence to a PPI in the comparator arms of the model with lower adherence assumed to result in an increase in upper GI adverse events. Quality of life loss and resource use associated with adverse events were also taken from the NICE model.

The results of the analysis were:

Naproxen/esomeprazole versus	Incremental cost	Incremental Quality adjusted life years (QALYs)	Incremental cost per QALY
Naproxen + generic PPI	£420	0.0255	£16,465
Diclofenac + generic PPI	£628	0.0580	£10,817
Ibuprofen + generic PPI	£324	0.0781	£4,155

The key limitations of the analysis were:

- No data were presented comparing naproxen/esomeprazole with any of the comparators. In addition, a formal indirect comparison was not conducted.
- The adverse event rates taken from the NICE model for each of the comparator treatments were not based on statistically significant differences. When the non-significant differences were removed the incremental cost-effectiveness ratios (ICERs) changed to £18k per QALY vs ibuprofen and £8k per QALY versus diclofenac.
- The patient population in which the adverse event data were obtained did not reflect the patient group being considered in the submission. As such, some adjustments had to be made to the NICE data for use in the model.
- The lower adherence rate with the NSAID + generic PPI treatments was based on an unpublished retrospective study with a number of limitations. The study used the percentage of NSAID-treated days covered by a PPI prescription as a proxy for adherence, the patients in the study were not confined to those aged ≥65 years and the

patients were not all on high-dose NSAIDs. As such, the adherence rate used in the model is uncertain.

- The model results were sensitive to the assumed lower adherence rate of the comparator treatments. A threshold analysis showed that for the comparison with naproxen + generic PPI the cost per QALY increased to £30k when the adherence rate was increased to 0.85 (base case rate was 0.73).
- In a scenario analysis where the non-significant differences were removed and a more conservative relationship between lower adherence and increase in adverse events was assumed, the ICERs were £32k, £55k and £10k per QALY vs naproxen, ibuprofen and diclofenac respectively.

Due to weaknesses of the clinical data and uncertainty associated with the adherence rate used in the model, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from Arthritis Care in Scotland.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guidelines, SIGN 123: Management of early rheumatoid arthritis, in February 2011. These guidelines recommend that "the lowest NSAID dose compatible with symptom relief should be prescribed" and gastro-protection should be introduced for patients with RA at risk of NSAID-associated gastro-duodenal ulcers".

The National Institute for Clinical Excellence (NICE) published national clinical guidelines for the care and management of osteoarthritis in February 2008, and for the management and treatment of rheumatoid arthritis in adults in February 2009. Both guidelines recommend that oral NSAIDs/COX-2 inhibitors be used at the lowest effective dose for the shortest possible period of time and that the lowest acquisition cost PPI be co-prescribed.

Additional information: comparators

NSAID and proton pump inhibitor (PPI) given separately. Those detailed within the submission are: generic naproxen 1,000 mg daily + generic PPI, generic diclofenac 150 mg daily + generic PPI, generic ibuprofen 2,400 mg daily + generic PPI.

SMC has not recommended esomeprazole for the prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Naproxen/esomeprazole (Vimovo)	**500mg/20mg twice daily**	**182**
NSAID plus PPI prescribed separately		
Naproxen or naproxen EC plus esomeprazole	500mg twice daily plus 20mg daily	286 to 310
Naproxen or naproxen EC plus omeprazole	500mg twice daily plus 20mg daily	67 to 91
Naproxen or naproxen EC plus lansoprazole	500mg twice daily plus 15 to 30 mg daily	63 to 97
Diclofenac plus esomeprazole	50mg three times daily plus 20mg daily	259
Diclofenac plus omeprazole	50mg three times daily plus 20mg daily	40
Diclofenac plus lansoprazole	50mg three times daily plus 15 to 30mg daily	36 to 46

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 15th August 2011.

Additional information: budget impact

The submitting company estimated that around 20,000 patients ≥65 years are receiving an NSAID and of these around 50% were assumed to be prescribed a PPI. Based on an estimated uptake of 0.1% in year 1 (17 patients) and 7.4% in year 5 (1,304 patients) and a discontinuation rate of 13%, the impact on the medicines budget was estimated at £839 in year 1 rising to £65k in year 5. Assuming some displacement of existing NSAIDs and generic PPIs the net medicines budget impact was estimated at £530 in year 1 and £41k in year 5.

References

The undernoted references were supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 16 September 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.