

Re-Submission

aprepitant 80mg, 125mg hard capsules (Emend®) SMC No. (242/06)

Merck, Sharp & Dohme Ltd

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 resubmission

aprepitant (Emend®) is not recommended for use within NHS Scotland.

Indication under review: As part of combination therapy, for prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Compared with a control regimen, aprepitant has been shown to increase the proportion of patients achieving a complete response in a study of breast cancer patients or experiencing no vomiting in patients with a range of tumour types, when patients were initiated on their first cycle of a moderately emetogenic chemotherapy regimen. However the control regimen was considered suboptimal for the treatment of delayed symptoms and evidence for use in subsequent cycles is limited.

Overall the submitting company did not present sufficiently robust clinical and economic analyses to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

As part of combination therapy, for prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Dosing Information

Aprepitant 125mg capsule orally one hour before start of chemotherapy on day one and 80mg capsule once daily on days two and three.

Aprepitant is given for three days as part of a regimen that includes a corticosteroid and a 5-hydroxytryptamine (5-HT) antagonist.

Product availability date

April 2005

Summary of evidence on comparative efficacy

Aprepitant is an oral substance P, neurokinin 1 (NK-1)-receptor antagonist that binds to the NK-1 receptor which has been associated with numerous inflammatory conditions, mediation of the emetic reflex and modulation of central nervous system disorders.

Aprepitant has previously been accepted for restricted use by the Scottish Medicines Consortium (SMC) for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy. The indication under review is for an extension to this indication to include prevention of nausea and vomiting associated with moderately emetogenic cancer (MEC) chemotherapy. The submitting company has requested that the SMC considers the use of this product when positioned for use in breast cancer patients only.

The evidence is based on two double-blind, phase III studies with a duration of 120 hours after the initiation of MEC chemotherapy. One study was in adult patients with a range of tumour types and chemotherapy regimens (protocol 130) and one in breast cancer patients being treated mainly with an anthracycline plus cyclophosphamide (AC) regimen (protocol 071). Included patients were to be naïve to either moderate or highly emetogenic chemotherapy, have a Karnofski score of ≥ 60 and a life expectancy of ≥ 4 months. The treatment regimens compared in both studies were administered orally. The aprepitant regimen was: day 1: aprepitant 125mg prior to chemotherapy, ondansetron 8mg (prior to chemotherapy and repeated 8 hours after first dose of chemotherapy) and dexamethasone 12mg prior to chemotherapy followed on days 2 and 3 by aprepitant 80mg daily. The control regimen was: day 1: ondansetron 8mg (prior to chemotherapy and repeated 8 hours after first dose of chemotherapy) plus dexamethasone 20mg prior to chemotherapy, followed on days 2 and 3 by ondansetron 8mg twice daily. The dose of dexamethasone was reduced in the aprepitant group as aprepitant is known to approximately double the serum level of dexamethasone when the two drugs are co-administered.

In the protocol 130 study, 848 patients were randomised using in-house blinding with stratification for gender to the aprepitant regimen (n=430) or the control regimen (n=418). Although patients suffering from a range of malignant tumours were included, approximately half had breast cancer. The primary outcome was the proportion of patients reporting no vomiting during the 120 hours (5 days) following the initiation of chemotherapy measured in the full analysis set (defined as those patients who received MEC, took a dose of study drug, and completed at least one post-treatment efficacy assessment). For the primary outcome, patients recorded the time and date of nausea and vomiting episodes in a diary. A vomiting episode was clearly defined in the study protocol, nausea was assessed daily using a 100mm visual analogue scale (VAS: 0 mm is “no nausea”, 100 mm “nausea as bad as it could be”) and any rescue medication recorded. The primary outcome was analysed using a logistic regression model which included terms for treatment, gender, and investigative site.

Over the 120 hours of the study, no vomiting was reported in 76% (324/425) of patients in the aprepitant group and 62% (252/406) of patients in the control group. In the acute phase (0 to 24 hours), no vomiting was reported in 92% (390/424) of patients in the aprepitant group and 84% (340/406) of patients in the control group, and in the delayed phase (2 to 5 days), in 78% (331/425) versus 67% (272/407) of patients, respectively.

One of the key secondary outcomes, the proportion of patients reporting overall complete response, defined as no emetic episodes and no use of rescue medication, during the 120 hours after initiation of chemotherapy was significantly greater in the aprepitant group (69% [292/425] versus 56% [229/407], $p < 0.001$).

A protocol-specified analysis was conducted for breast and non-breast cancer patients, using a logistic regression model that included terms for treatment, gender and centre. This analysis included 218 patients from the aprepitant group and 220 patients from the control group. Most of these patients received AC-based chemotherapy (around 87%). Over 120 hours, no vomiting was reported by 69% (151/218) and 53% (116/220) of aprepitant and control patients, respectively, with a complete response reported by 63% (138/218) and 46% (102/220) of patients.

In the protocol 071 study, 866 breast cancer patients scheduled for their first treatment with AC-based chemotherapy were randomised to the aprepitant regimen (n=438) or the control regimen (n= 428). The primary outcome was the proportion of patients reporting complete response, defined as no vomiting and no use of rescue therapy, during the overall phase (0 to 120 hours) after initiation of MEC, measured in the modified intention to treat population (defined as those patients who were receiving chemotherapy, received at least one dose of study drug, and completed at least one post-treatment assessment on day 1). A logistic regression model was used for the comparison between aprepitant and the control regimens which included terms for treatment allocation, investigator group and age category. All components of the primary and secondary outcomes were measured as for the protocol 130 study.

Over the 120 hours, a complete response was reported by significantly more aprepitant patients than control patients (51% [220/438] versus 42% [180/424], $p=0.015$). In the acute phase, a complete response was reported in 76% of aprepitant patients and 69% of control patients and in the delayed phase in 55% and 49% of patients respectively. The difference was statistically significant for the acute phase but did not reach statistical significance for the delayed phase.

Having no vomiting was reported as a secondary outcome and was significantly more frequent for the aprepitant group for the overall, acute and delayed phases. Over the 120 hours, 76% (327/432) in the aprepitant group compared with 59% (249/424) of patients in the control group reported no vomiting. In the acute phase, no vomiting was reported in 88% versus 77% of patients and, in the delayed phase, in 81% versus 69% of patients for the aprepitant and control groups, respectively.

The Functional Living Index–Emesis (FLIE) questionnaire recorded the impact on daily living and found significantly more patients in the aprepitant than in the control group reported minimal or no impact on daily living (63.5% versus 55.6%, $p=0.019$). When broken down to the individual components of vomiting and nausea, the difference in FLIE score was significant for the vomiting component only.

Summary of evidence on comparative safety

No new or unexpected adverse events were reported with aprepitant in either of the clinical studies. There were similar rates of drug-related adverse events in the aprepitant and control groups.

Aprepitant may interact with a range of drugs including warfarin (monitoring of the INR for the 2 weeks following aprepitant treatment is recommended for patients on chronic warfarin therapy) and oral chemotherapeutic agents (caution is advised and additional monitoring may be appropriate in patients receiving such agents which are metabolised primarily or in part by CYP3A4).

Summary of clinical effectiveness issues

Chemotherapy agents defined as moderately emetogenic relevant to the patient population under review include taxanes, doxorubicin, epirubicin, intermediate and low doses of cyclophosphamide and carboplatin. Aprepitant has been shown to increase the proportion of patients achieving a complete response or experiencing no vomiting compared with the control regimen, in patients with a range of tumour types initiated on a moderately emetogenic chemotherapy regimen. The main benefit of aprepitant observed in both studies was the increase in the proportion of patients experiencing no vomiting throughout the 120 hours. An advantage in terms of reduction in the use of rescue medication or in the experience of significant or no nausea was less evident.

In this resubmission the submitting company has requested that the SMC considers the use of aprepitant when positioned for use in breast cancer patients only. Further to receipt of advice from the New Drugs Committee the company adjusted the proposed positioning to request that SMC consider use of aprepitant in patients with breast cancer who are receiving AC-based chemotherapy regimens only. The evidence for this positioning comes from the two pivotal

phase III studies. The protocol 071 study provides data for AC-based regimens specifically in breast cancer patients, and a pre-specified but unpublished subgroup analysis of the protocol 130 study provides data for AC and non AC-based regimens in breast cancer patients. However, the number of patients treated with non AC-based regimens was small and the evidence base is limited in Scotland.

The British National Formulary (BNF) states that dexamethasone, either used alone or in combination with metoclopramide or prochlorperazine, is the drug of choice for preventing delayed symptoms and that 5HT₃ antagonists may be less effective for delayed symptoms. The control regimen used in the two phase III studies did not reflect usual regimens used for CINV and was determined to be suboptimal by the European Medicines Agency (EMA). The omission of dexamethasone from day 2 onwards would be most likely to impact on delayed nausea and vomiting. Advice from experts contacted by SMC suggests that the control regimen does not reflect regimens commonly used in clinical practice in Scotland.

Patients recruited to both studies were required to be naïve to MEC or highly emetogenic chemotherapy. Therefore, the efficacy of the aprepitant regimen is untested in patients who may have experienced nausea and vomiting with a previous chemotherapy regimen, and the impact on the response to aprepitant of the anticipatory effect in previously poorly-controlled patients is not known. This may affect the generalisability of the results to clinical practice.

The efficacy of antiemetic therapy tends to diminish over subsequent cycles of chemotherapy. A multicycle extension to study protocol 071 allowed patients an option to continue their randomised treatment for a further two to four cycles. Patients continued to benefit from aprepitant but the EMA did not consider the methodology of this extension appropriate as patients who had a favourable outcome in cycle 1 were more likely to continue, thus introducing bias.

Summary of comparative health economic evidence

A cost utility analysis using a decision tree analysis was provided by the submitting company comparing an aprepitant regimen (aprepitant/dexamethasone/ondansetron pre-chemotherapy and aprepitant post-chemotherapy) to a standard therapy comparator for the prevention of emesis in breast cancer patients receiving a cycle of moderately emetic chemotherapy. Standard therapy consisted of dexamethasone/ondansetron pre-chemotherapy and dexamethasone/domperidone post-chemotherapy. The comparator was appropriate for Scottish clinical practice.

The model consisted of three health outcomes: complete protection (no emesis or rescue therapy and limited nausea), complete response (no emesis or rescue therapy, but nausea experienced), inadequate response (some emesis or use of rescue therapy). These outcomes were applied to the acute (day 1) and delayed (days 2-5) phases of emesis with a cycle of chemotherapy. A 5-day time horizon was adopted for the assessment. The clinical data for the probabilities of being in each state over these phases was derived from individual patient data for a sub-group of breast cancer patients in the aprepitant protocol 130 study (representing 52% of patients in this study). Utility estimates for the three health states were 0.79 for complete protection, 0.594 for complete response and 0.27 for inadequate response, and were derived from published sources using a visual analogue scale to assess utilities associated with chemotherapy with or without vomiting and nausea. Use of rescue medication and all

resource- use data including hospitalisations relating to emesis were derived from the individual patient data in the breast cancer sub-group of study 130.

The base case result was an incremental cost per quality adjusted life year (QALY) gained for the aprepitant regimen of £14,610 compared to the standard therapy regimen. This was based on a net incremental cost of £13.87 and 0.35 quality adjusted life days (which equates to 0.00096 QALYs). The net costs consisted of an incremental drug cost of £51.22 per patient for the aprepitant regimen, but savings primarily associated with reduced hospital days (of -£36.32 per patient). There was also a small saving in rescue medication costs with the aprepitant regimen (-£0.52 per patient).

There were several weaknesses in the economic analysis related to limitations in the clinical study evidence base and other uncertainties in key parameters:

- The efficacy of the comparator regimen may have been underestimated as the regimen used in the aprepitant trials was sub-optimal. The manufacturer used an appropriate comparator regimen, but assumed this had the same efficacy as that for the breast cancer sub-group of the 130 study. Because of this, the cost-effectiveness of aprepitant is uncertain and may have been overestimated. Sensitivity analysis provided by the company showed that when the efficacy of the comparator regimen was increased by 10% and 20% the ICERs increased to £26k and £49k per QALY respectively.
- A key weakness was that data from study 071 was not included in the economic analysis even though this was in women with breast cancer receiving AC-based regimens, the positioning sought by the manufacturer. It is uncertain what impact its inclusion would have on the cost-effectiveness results.
- The cost-effectiveness of aprepitant was assessed for a single chemotherapy cycle only, hence cost-effectiveness over multiple chemotherapy cycles is uncertain. Also, the data are predominantly in patients receiving AC-based chemotherapy, hence cost-effectiveness across a range of MEC chemotherapies or in non-AC based chemotherapy is uncertain.
- The resource use data included in the economic analysis were also from the 130 study breast cancer sub-group which included no UK centres, so the representativeness of the estimates for Scotland clinical practice is uncertain. The main cost saving estimated with aprepitant was for hospitalisations, which was zero for aprepitant and 0.069 hospital days per patient for standard therapy. SMC clinical experts who were consulted indicated there would be very few hospital admissions associated with current regimens, especially after the first cycle of chemotherapy. However, cost-effectiveness was highly sensitive to this parameter - reducing the hospitalisation days for standard therapy by half or alternatively assuming no difference in hospitalisations increases the ICER to over £33K/QALY and over £50K/QALY respectively.
- The utility estimates for the health states in the economic analysis are derived from a study with fairly weak methodology. However, based on SMC clinical expert feedback the utility value of 0.27 for the inadequate response health state can be considered plausible for the short term quality of life impact of emesis.

As a result of these weaknesses and uncertainties the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

Ondansetron, granisetron, domperidone, metoclopropamide, dexamethasone. In practice comparator regimens usually include a combination of drugs (eg combinations of ondansetron, dexamethasone and domperidone over 5 days are commonly used in Scotland for MEC).

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Combination regimens		
Aprepitant	125mg on day 1 followed by 80mg on days 2 and 3	
Dexamethasone Ondansetron	In combination as per clinical study: 12mg on day 1 8mg before and 12 hours after chemotherapy	59
Ondansetron Dexamethasone	8mg before chemotherapy 8mg before chemotherapy then 2mg three times daily on days 2 to 5	
Domperidone	20mg three times daily for 3 to 5 days	10
Individual drugs		
Aprepitant	125mg on day 1 followed by 80mg on days 2 and 3	47
Ondansetron	8mg before chemotherapy then 8mg every 12 hours up to 5 days	54
Granisetron	2mg before chemotherapy then 2mg daily during treatment up to 5 days	52
Domperidone	20mg three times daily for 3 to 5 days	2.71
Metoclopropamide	20mg three times daily for 3 to 5 days	1.87
Dexamethasone	In combination with other anti emetics: 8mg daily up to 3 days	<1

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 2 August 2011. All drugs are given orally. In practice comparator regimens usually include a combination of drugs listed in the table above, one sample regimen is included.

Additional information: budget impact

The submitting company estimated the population eligible for treatment currently to be 1,946 people with breast cancer receiving moderately emetic chemotherapy, rising to 2,173 by year 5. This is based on an estimate of 41% of patients with invasive breast cancer in Scotland assumed to be receiving moderately emetic adjuvant chemotherapy, and 1% of advanced breast cancer patients receiving MEC. All patients receiving MEC are assumed to be treated with anti-emetic therapy. Based on an estimated uptake of aprepitant of 8% in year 1 (156 patients), and 22% in year 5 (478 patients), the impact on the medicines budget was estimated at £37K in year 1 and £113K in year 5 assuming patients are treated with anti-emetic therapy for 5 cycles of chemotherapy. The net impact after displacement of dexamethasone and domperidone is estimated to be £34K in year 1 and £106K in year 5. Resource savings of £81 in year 1 rising to £249 in year 2 were estimated due to a reduction in the use of rescue medicine by patients treated with aprepitant.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

Rapoport BL, Jordan K, Boice JA et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. *Support Care Cancer* 2010 18:423-31

Warr DG, Hesketh PJ, Gralla RJ et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *Journal of Clinical Oncology* 2005;23:2822-2830.

MSD Data on File. PN130 - Analysis of breast and non-breast cancer populations. 2011.

Herrstedt J, Muss HB, Warr DG et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer* 2005;104:1548-1555.

European Medicines Agency. European Public Assessment Report for Emend

British National Formulary (BNF 61) March 2011

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.