Scottish Medicines Consortium

aprepitant 125mg, 80mg capsules (Emend®)

Merck Sharp and Dohme Ltd **No. 242/06**

New indication: prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy

10 February 2006

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

Aprepitant (Emend®) as part of combination therapy is not recommended for use within NHS Scotland for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

The aprepitant regimen showed a significant difference compared to the standard regimen in terms of the primary end-point of complete response for the acute phase only. No superiority for the aprepitant regimen could be demonstrated for the prevention of nausea.

The economic case for aprepitant in the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Aprepitant 125mg, 80mg capsules (Emend®)

Indication

Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. Aprepitant is given as part of combination therapy.

Dosing information

Day 1: aprepitant 125mg oral 1 hour before chemotherapy
Day 2 and 3: aprepitant 80mg oral in the morning
Aprepitant is given as part of a regimen that includes a corticosteroid and a $5HT_3$ receptor antagonist (see aprepitant regimen used in clinical trial in "cost of relevant comparators" section, below).

UK launch date

28 April 2005

Comparator medications

US and European guidelines on the prevention of chemotherapy induced nausea and vomiting (CINV) for moderately emetogenic chemotherapy recommend a range of regimens using various combinations of anti-emetics including 5 hydroxytryptamine-3 ($5HT_3$) receptor antagonist, metoclopramide, dexamethasone and aprepitant (in one guideline).

Cost of relevant comparators

Drug	Dose	Cost per cycle (£)
Aprepitant regimen		
Aprepitant	125mg po on day 1 then 80mg on days 2 and 3	62
Dexamethasone	12mg po on day 1	
Ondansetron	8mg po bd on day 1	
Standard regimen ***(used in clinical study)***		
Dexamethasone	20mg po on day 1	44
Ondansetron	8mg po bd on day 1-3	

po; per oral.
Costs obtained from the British National Formulary (edition 50) September 2005 and the eVADIS database (accessed on 22/11/05).

Summary of evidence on comparative efficacy

Aprepitant is a neurokinin 1 (NK-1) receptor antagonist. NK-1 receptors have been associated with inflammatory conditions, mediation of the emetic reflex and modulation of central nervous system disorders.

One prospective, double-blind, double-dummy parallel-group study has been conducted in patients with breast cancer being treated with moderately emetogenic chemotherapy (MEC) that included cyclophosphamide. Patients =18 years, naïve to emetogenic chemotherapy

(Hesketh Level = 3) and due to receive the first course of MEC were included in the study. MEC included intravenous (IV) cyclophosphamide 750-1500mg/m^2; IV cyclophosphamide 500-1500mg/m^2 + IV doxorubicin = 60mg/m^2 or IV cyclophosphamide 500-1500mg/m^2 + IV epirubicin = 100mg/m^2. Other chemotherapy agents with Hesketh level = 2 were allowed. Patients were also required to have a Karnofsky score = 60 (on a scale of 0 to 100, with high scores indicating better performance status) and a predicted life expectancy of = 4 months. Exclusion criteria included symptomatic central nervous system (CNS) malignancy, radiation treatment to abdomen or pelvis within one week of treatment, presence of an active infection (including systemic fungal infection) severe illness excluding malignancy, abnormal laboratory values, vomiting in the preceding 24 hours or use of an antiemetic (except single doses of lorazepam in preceding 48 hours) and current treatment with a corticosteroid.

Patients were randomised to the aprepitant regimen or the standard regimen. Matching placebo capsules were used. The doses of dexamethasone reflected the known interaction between aprepitant and dexamethasone which results in dexamethasone levels being increased by approximately two-fold. Rescue medication permitted included 5-HT_3 receptor antagonists, corticosteroids and domperidone.

The primary end-point used to evaluate efficacy was the proportion of patients reporting a complete response (CR), defined as no vomiting and no use of rescue medication, from 0 to 120 hours after MEC. Patients completed a diary (from 0-120 hours) which included the date and time of any emetic episode and use of rescue medication and daily nausea ratings (on a 100mm visual analogue scale (VAS): 0=no nausea and 100=nausea as bad as it could be) after the first cycle of chemotherapy. The proportion of patients with CINV which had no or minimal impact on daily life assessed by the Functional Living Index-Emesis (FLIE) questionnaire was a secondary end-point. The FLIE questionnaire has two nine-item domains (nausea and vomiting) with each item scoring a maximum of 7 points. Minimal or no impact of CINV on daily life was defined as a total score of >108 or a domain score >54. The FLIE was completed pre-chemotherapy and on day 6. Exploratory endpoints included CR in the acute (0-24 hours) and delayed phases (24-120 hours) and proportion of patients reporting no significant nausea (VAS < 25mm) and no nausea (VAS < 5mm).

The modified intention-to-treat population used in the efficacy analysis comprised 433 and 424 patients in the aprepitant and standard groups, respectively. The percentage of patients with an overall CR in the aprepitant and standard groups were 51% and 42% (p=0.015) respectively. More patients in the aprepitant group compared with the standard group had a CR in the acute phase (76% v 69%, p=0.034), although in the delayed phase the difference was not significant (55% v 49%, p=0.064). There were no significant differences between the aprepitant and standard groups in terms of patient reporting of nausea. The percentage of patients with a FLIE total score indicating no or minimal impact of emesis on daily living were 64% and 56% for the aprepitant and standard groups respectively (p=0.019). There was a significant difference in favour of aprepitant for the vomiting domain (86% v 72%; p<0.001) but not for the nausea domain score (54% v 51%).

Patients who successfully completed cycle 1 were eligible to continue into a multiple-cycle extension study where they received the same antiemetic regimen to which they were randomised in cycle 1 for a further three cycles. CR was assessed as in cycle 1. Of the 866 patients recruited into the initial study 744 (86%) entered the multiple-cycle extension and 650 (75%) completed all 4 cycles. Analysis of sustained CR was performed using Kaplan-Meier methods and analysis of CR by cycle used a transitional probabilities approach. The cumulative percentage of patients who had a CR in cycle 1 and sustained a CR over cycles 2-4 was higher in the aprepitant group compared with the standard group (p=0.017) although the difference was significant for the no vomiting component only when the components of

the CR were analysed separately. The CR rate differences (aprepitant regimen – standard regimen) for cycles 1, 2, 3 and 4 were 8.3%, 14.4%, 14.8% and 16.6%, respectively.

Summary of evidence on comparative safety

There were similar rates of drug-related adverse events in the aprepitant and standard groups (22% v 20% respectively) and only fatigue was reported more frequently in the aprepitant group compared with the standard regimen. Overall, no new or unexpected adverse events were reported with aprepitant in the clinical study.

Aprepitant is a substrate, a moderate inhibitor and an inducer of CYP3A4 and is also an inducer of CYP2C9. 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 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

The proportion of females recruited in the clinical study was 99.8% and the extrapolation of efficacy of aprepitant in prevention of emesis in men has been questioned. The scientific discussion of the European Public Assessment Report (EPAR) noted that although the female gender is a risk factor for development of nausea and vomiting, female gender is not thought to influence the relative efficacy of antiemetic regimens. It concluded that there is no indication that the product will not have an effect in men.

The appropriateness of the standard regimen where no corticosteroid was used after day 1 has been questioned in the scientific discussion of the EPAR. In addition, the authors of the clinical study concluded that the trial data provide a foundation for refinement of the aprepitant regimen potentially by increasing the duration of concomitant 5-HT_3 receptor antagonist and/or corticosteroid.

The European Medicines Agency (EMEA), in the scientific discussion of the EPAR, criticised the design of the multiple extension trial and indicated that re-randomisation prior to cycle 2 would have been appropriate.

Summary of comparative health economic evidence

The manufacturer's submission modelled an aprepitant regimen to the standard comparator regimen in line with the randomised control trial. The model had three health outcome definitions:

1. "**Complete Protection**" = no emesis, no rescue therapy and a maximum nausea VAS score <25 mm on a 100 mm VAS with 0 = "no nausea" and 100 = "nausea as bad as it can be".
2. "**Complete Response**" = no emesis and no rescue therapy
3. "**Incomplete Response**" = some emesis or rescue therapy

The utilities for each were 0.90, 0.70 and 0.20 respectively and were derived from three chemotherapy-specific studies. Drug and other resource use was based on the randomised control trial and was valued using appropriate sources.

The incremental cost per QALY (ICER) was £27,960 and probabilistic sensitivity analyses showed a 63% chance that the ICER was <£30,000.

A critical appraisal of the model and parameters raises the following issues:

- The trial measured impact of CINV on daily life using a functional living questionnaire. This showed a total score of 64% for aprepitant and 56% for control. These differences suggest the utilities used may not be appropriate for these health states. A literature search identified four breast cancer states with utility values of 0.2 or lower, these being:
  - breast cancer, high dose chemotherapy, with bone marrow transfusion 0.1
  - recurrent metastatic breast cancer, anthracycline-resistant chemotherapy, terminal disease 0.16
  - breast cancer, terminal duration 1 month 0.19
  - recurrent metastatic breast cancer, anthracycline-resistant chemotherapy, sepsis 0.2.

  This suggests a value of 0.20 for incomplete response could be too low and has not been justified by the manufacturer.

- The comparator is not necessarily representative of Scottish practice, e.g. if dexamethasone only was used for delayed CINV then the cost of the comparator would be considerably less than the standard regimen used in the trial (£28 versus £44).
- Clinical data are from the first chemotherapy cycle and it is uncertain that these will generalise to subsequent cycles. Clinical data for the subsequent 3 cycles were provided but the impact on the base case result of using the 4-cycle data is not known.
- The trial concluded that further research is needed to refine the aprepitant regimen, so the clinical base is limited.
- The modelled endpoints may have introduced bias; the primary end point from the randomised control trial was CR (i.e. no emesis and no rescue therapy) but the model divided this into complete response and complete protection using data from one of five secondary endpoints.
- The sensitivity analyses were not sufficient to address these concerns, particularly around utility values.

The economic case has not been demonstrated.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer estimated the drug budget impact at £107K in year 1 rising to £537K in year 5. This assumes that 10% of 4300 eligible patients (430) will receive aprepitant in year 1 rising by 10% per year.

Additional information

On 8 November 2004 following a full submission the SMC accepted aprepitant (Emend) for restricted use within NHS Scotland for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy. It should be initiated only by appropriate hospital-based specialists.

On 7 November 2005 following a full submission the SMC accepted palonosetron for use within NHS Scotland for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. The SMC noted that palonosetron is as effective as other anti-emetics in preventing emesis when given as a single intravenous injection following highly emetogenic chemotherapy in the acute phase and moderately emetogenic chemotherapy in the acute and delayed phases post-chemotherapy.

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 16 January, 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

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

1. *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.*

2. *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.*

3. *European Medicines Agency. European Public Assessment Report; Emend-H-527-II-09 Scientific Discussion. Accessed on 15/11/05: http://www.emea.eu.int/humandocs/Humans/EPAR/emend/emend.htm*