Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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aprepitant, 80mg, 125mg hard capsules and 125mg powder for oral suspension (Emend®) SMC No (1241/17)

Merck, Sharp & Dohme Limited

05 May 2017

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

aprepitant (Emend®) is accepted for use within NHS Scotland.

Indication under review: As part of combination therapy, for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in infants, toddlers and children from the age of six months to less than 12 years (powder for oral suspension) and adolescents from the age of 12 years to 17 years (hard capsules).

A randomised, double-blind, placebo-controlled study demonstrated that the addition of aprepitant to a $5HT_3$ receptor antagonist (+/- steroid) in children and adolescents receiving chemotherapy with a moderate to very high emetogenic risk produced a significant anti-emetic benefit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 12 June 2017

Indication

For the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy (MEC) in infants, toddlers and children from the age of six months to less than 12 years (powder for oral suspension) and adolescents from the age of 12 years to 17 years (hard capsules). Aprepitant is given as part of combination therapy.[1, 2]

Dosing Information

Aprepitant is administered orally once daily for three days as part of a regimen that includes a $5HT_3$ antagonist.

- Children between six months and 12 years (and not less than 6kg): weight-based dose of powder for oral suspension (see summary of product characteristics [SPC] for details).
- Adolescents (12 to 17 years): one 125mg capsule on day 1 and one 80mg capsule on days 2 and 3. Capsules should be swallowed whole.

Aprepitant is administered one hour prior to chemotherapy on days 1, 2 and 3. If no chemotherapy is given on days 2 and 3, aprepitant should be administered in the morning. See SPC for chosen $5HT_3$ antagonist for appropriate dosing information. If a corticosteroid, such as dexamethasone, is co-administered with aprepitant, the dose of the corticosteroid should be administered at 50% of the usual dose.[1, 2]

Product availability date

December 2015 (hard capsules)
September 2016 (powder for oral suspension)

Summary of evidence on comparative efficacy

Aprepitant is an antagonist at human substance P neurokinin 1 receptors.[1, 2] This submission relates to the use of aprepitant as part of combination therapy for the prevention of nausea and vomiting associated with MEC in children and adolescents from the age of six months to 17 years. Aprepitant is also indicated for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy (HEC) in children and adolescents from the age of six months to 17 years.[1,2] The HEC indication in children and adolescents is the subject of an abbreviated submission to SMC. SMC has previously accepted aprepitant for use in adults receiving HEC (132/04), but not for adults receiving MEC (242/06).

The evidence for the indication under review is from a phase III, randomised, double-blind, placebo-controlled study, P208, which recruited patients between six months and 17 years of age, with documented malignancy, who were scheduled to receive MEC, HEC, or very highly emetogenic chemotherapy (VHEC), or had previously not tolerated chemotherapy due to vomiting. Patients were expected to receive ondansetron as part of an anti-emetic regimen. They were required to have a Karnofsky score ≥60 if older than 10 years or a Lansky Play performance score ≥60 if 10 years or younger. Life expectancy was at least three months.[3]

Patients were randomised equally to receive treatment with oral aprepitant plus ondansetron, or placebo plus ondansetron. Double-blind study treatment was administered for the first three days of the first cycle of chemotherapy and patients were assessed in a double-blind manner for 120 hours.[3]

Randomisation was stratified according to:

- age: six months to less than two years, two to less than six years, six to less than 12 years, or 12 to 17 years
- planned use of VHEC (>90% risk of emetogenicity)
- planned use of dexamethasone as an anti-emetic [3]

The dose of aprepitant (powder for oral suspension) was weight-based for children younger than 12 years: 3mg/kg on day 1 and 2mg/kg on days 2 and 3. Adolescents from 12 to 17 years received one 125mg capsule on day 1 and one 80mg capsule on days 2 and 3.[3] Aprepitant was administered one hour before chemotherapy on day 1 and in the morning on days 2 and 3 (or one hour before chemotherapy if that was administered on day 2 or 3). Ondansetron (dosing and route according to licensed indication or local practice) was administered on day 1 and only on day 2 or 3 if chemotherapy was administered that day. Dexamethasone was administered (intravenously) at the discretion of the investigator. Patients in the aprepitant group who received dexamethasone were given 50% of the usual dose (in a blinded manner) due to a pharmacokinetic interaction between the two drugs. Rescue medications were allowed at the discretion of the investigators to alleviate established nausea and vomiting.[3]

The primary outcome was the proportion of patients who achieved a complete response (defined as no vomiting, no retching and no use of rescue medication) between 25 and 120 hours (delayed phase) after initiation of emetogenic chemotherapy.[3] The primary analysis was in the intention to treat (ITT) population (n=302), defined as all randomised patients who received at least one dose of study medication. It excluded five randomised patients who did not receive study medication.[4] The primary outcome was achieved in significantly more aprepitant than control patients: 51% (77/152) versus 26% (39/150) ($p<0.0001$).[3]

The secondary outcome of complete response in the acute phase (0 to 24 hours) was achieved in 66% (101/152) of aprepitant patients versus 52% (78/150) of control patients ($p<0.05$); and in the overall period (0 to 120 hours) in 40% (61/152) versus 20% (30/150) ($p<0.01$), in the respective groups.[4] The proportion of patients with no vomiting regardless of rescue medication was significantly higher in the aprepitant versus control group: 71% versus 53% in the acute phase; 55% versus 28% in the delayed phase and 47% versus 21% in the overall period.[4] The estimated median time to first vomiting (exploratory outcome) was 96 hours in aprepitant patients versus 28 hours in control patients, a difference of 68 hours which is statistically significant ($p<0.0001$) and a clinically relevant benefit. The primary outcome treatment effect (aprepitant versus control) was higher in patients receiving single day chemotherapy (81% [21/26] versus 31% [5/16]) compared with longer chemotherapy regimens (44% [56/126] versus 25% [34/134]).[4]

The size of the subgroup representing the population under review (patients who received MEC) is not known. Moderate risk of emesis was defined as 30% to 60%, high risk as 60% to 90% and very high risk as >90%, based on known frequency of nausea and vomiting in the absence of an anti-emetic. Patients were stratified according to use of VHEC versus MEC/HEC. The proportion of patients that received either MEC or HEC was 34% (102/302).[3] No data are available for the target MEC subgroup. In the MEC/HEC subgroup, 66% (35/53) of aprepitant patients achieved the primary outcome (complete response in the delayed phase) compared with 39% (19/49) of control patients. Complete response in the acute phase (0 to 24 hours) was achieved in 70%

(37/53) of aprepitant patients versus 55% (27/49) of control patients, and in the overall period (0 to 120 hours) in 49% (26/53) versus 33% (16/49) of the respective groups in the MEC/HEC subgroup.[4]

Summary of evidence on comparative safety

The rate of adverse events was similar in the aprepitant and control groups: 79% (120/152) and 77% (116/150). Serious adverse events were reported in 30% (46/152) and 27% (41/150) of aprepitant and control groups.[3]

Apart from vomiting, the most commonly reported adverse events were anaemia (17% in aprepitant group versus 25% in the placebo group), febrile neutropenia (16% in both groups), and neutropenia (14% versus 12%). The most common grade 3 or 4 adverse events reported were febrile neutropenia (16% versus 14%), anaemia (9% versus 17%), and reduced neutrophil count (7% versus 11%) and rates in the aprepitant group were similar or lower than in the control group. The most common serious adverse event was febrile neutropenia, reported in 15% of patients in each treatment group.

Adverse events considered to be related to study drugs (aprepitant or ondansetron) were reported in 3.3% (5/152) of patients in the aprepitant group (hiccups, *Clostridium difficile* infection, vomiting, constipation, decreased blood calcium and potassium concentrations, and electrocardiogram T-wave inversion) and in 2.0% (3/150) of patients in the control group (increased alanine and aspartate aminotransferase levels [two each] and nausea). Two of the treatment-related adverse events in patients receiving aprepitant (*Clostridium difficile* infection and electrocardiogram T-wave inversion) were deemed to be serious adverse events. [3]

The SPC includes information on interactions of aprepitant with other drugs, including dexamethasone. [1, 2]

Summary of clinical effectiveness issues

Nausea and vomiting are extremely distressing adverse effects of chemotherapy, especially in paediatric patients, and the anxiety they induce may delay or reduce the dosage of planned chemotherapy regimens for subsequent cycles.[4] Clinical expert advice sought by SMC is that physicians usually prescribe ondansetron during chemotherapy and for 24 hours after the last dose of chemotherapy, with dexamethasone or metoclopramide. If ondansetron and dexamethasone or metoclopramide are insufficient, they may add another agent such as lorazepam or levomepromazine.

The pivotal study demonstrated that the addition of aprepitant to a regimen of ondansetron (±dexamethasone) in children and adolescents receiving chemotherapy with a moderate to very high emetogenic risk almost doubled (51% versus 26% in the aprepitant and control groups) the proportion of patients with no vomiting, no retching and no use of rescue medication in the delayed phase.[3] The primary outcome was originally to have assessed the overall (i.e. acute and delayed) phase (0 to 120 hours), but was amended during the study to assess the delayed phase, on advice from the US Food and Drug Administration.[4] The complete response benefit was smaller in the acute phase (0 to 24 hours): 66% versus 52% in the aprepitant and control groups. Over both acute and delayed phases, the complete response was 40% versus 20%, in the respective

groups. The proportion of patients who received concomitant dexamethasone was 28% and 29% in the aprepitant and control groups, respectively.[4]

The study has some limitations. There are limited comparative data versus the relevant anti-emetic regimens used in Scottish practice which may include ondansetron during and for 24 hours after chemotherapy has finished, in addition to dexamethasone or metoclopramide. A minority of patients received MEC and analysis of this subgroup was not possible, therefore the benefit of aprepitant in this patient population at lower risk of emesis is not known. Most patients received VHEC and the proportion of study patients that received HEC or MEC was 34%. The published report notes that it was not possible to classify patients according to receipt of HEC or MEC separately because several chemotherapy regimens are classified on the basis of body surface area, which could not be calculated for all patients. Another limitation is that only one cycle of chemotherapy was evaluated in a controlled manner. Furthermore, the use of dexamethasone and of rescue medication was not controlled.[3] Also, fewer patients in the aprepitant group versus control group had chemotherapy on more than one day: 83% (126/152) versus 89% (134/150).[4] Longer chemotherapy regimens in the control group may have biased results in favour of aprepitant. Multiple days of chemotherapy is known to be a risk factor for poorer control of emesis in adults.[5].

Aprepitant is an oral treatment and would not be appropriate if the patient is vomiting.

In general, clinical experts consulted by SMC considered that the place in therapy of aprepitant might be for refractory nausea and vomiting with standard anti-emetic treatment regimens in patients receiving MEC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing aprepitant in combination with ondansetron to ondansetron alone for the prevention of nausea and vomiting associated with MEC in children, toddlers and infants from the age of 6 months to less than 12 years, and in adolescents from the age of 12 to 17 years. Dexamethasone was included for 28% and 29% of patients in the aprepitant plus ondansetron and ondansetron treatment arms respectively, based on use in the pivotal study. SMC experts have indicated that the ondansetron is used in Scotland, however other treatments, including metoclopramide, are also available.

The company submitted a decision tree model which consisted of two phases: an acute phase (0-24 hours after chemotherapy initiation) and a delayed phase (25 to 120 hours after chemotherapy initiation). During the acute phase, patients were assessed for response at 24 hours and then classified as having either a complete response or incomplete response. Costs and quality adjusted life years (QALYs) associated with these health states in the acute phase were accrued and then patients entered the delayed phase of the model. In the delayed phase, patients were again assessed for response. The time horizon used in the base case analysis was five days (from the initiation of chemotherapy), for the first cycle of chemotherapy only.

The clinical data used in the economic model were based on a subgroup within the pivotal study which included patients receiving MEC and HEC.[4] Patients moved through the model according to the probability of complete response. The probability of complete response (in both model phases) was estimated to be 49% and 33% for the aprepitant plus ondansetron treatment arm and the ondansetron treatment arm respectively.

The model captured medicine acquisition costs as well as the cost associated with an incomplete response. Patients with an incomplete response were assumed to require hospitalisation (paediatric admission for unexplained symptoms with complications and co- morbidities), a phone consultation and rescue medication. It is worth noting that for the purposes of resource use the company stratified incomplete responders into three subgroups according to whether vomiting occurred and rescue medication was used based on the proportions in the ITT population in the pivotal study. Several assumptions were used to estimate health state costs in the analysis. For example, 15% of patients with an incomplete response in the acute phase, who experienced vomiting and rescue medication, were assumed to be hospitalised, while in the delayed phase 2.5% of these patients were assumed to be hospitalised. Adverse event costs were not included in the analysis on the basis of similar adverse event profiles between treatments.

Utility values were taken from published literature.[6] The study used included 30 adult patients with a variety of cancer types including breast cancer and lung cancer. The visual analogue scale was distributed to patients who were asked to rate their quality of life for the period since last chemotherapy cycle i.e. 3-4 weeks and then assuming an absence of nausea or vomiting. Patients with a complete response had a utility value of 0.75 while those with an incomplete response had a utility value of 0.27. For each health state, the model estimated the 5 day utility based on the number of days spent in the acute phase and delayed phase.

Aprepitant in combination with ondansetron resulted in a base case incremental cost effectiveness ratio (ICER) of £2,743 versus ondansetron based on an incremental cost of £4.46 and an incremental quality-adjusted life-year (QALY) gain of 0.0016. The aprepitant treatment regimen was associated with higher medicine costs versus the comparator arm (£52 and £5 respectively) with non-medicine costs estimated to be lower in the aprepitant arm compared to the comparator arm (£29 compared to £71) respectively.

The company provided both one-way and scenario sensitivity analysis. The parameters most sensitive are presented in table 1, below.

Table 1: Key sensitivity analysis results

Sensitivity analysis	ICER
Probability of complete response in comparator arm for both acute and delayed phase increased to 46.80% from 32.65%	£34,684
Probability of complete response in the aprepitant arm for both acute and delayed phase reduced to 36.54% from 49.06%	£18,660
Stratification of incomplete responders is set to be the same as the aprepitant arm	£17,583
Probability of complete response in the comparator arm for the acute and incomplete response in delayed phase increased to 35.15% from 22.45%	£10,820
Number of hospitalisations (acute phase) reduced to 0.75 from 1 in the base case	£7,469
Probability of hospitalisation (acute phase) reduced to 11.3% from 15%	£6,997

There were a number of weaknesses in the analysis which include the following;

- The clinical data used to estimate the probability of response within the economic model were derived from a subgroup analysis within the pivotal study, which included patients receiving HEC and MEC. It is therefore unclear whether these results are likely to be generalisable to patients receiving MEC only. The sensitivity analysis results presented in the first two rows of table 1 showed the impact of altering the relative efficacy inputs, but it should be noted that this was achieved using the upper or lower bounds on the 95% confidence interval, and thus could be considered conservative in exploring the uncertainty in efficacy in the MEC population.
- There is some uncertainty regarding the stratification of incomplete responders and the use of different proportions for each treatment arm for the purposes of resource use estimation. Clinical data used to support the proportion of patients in each subgroup were derived from the ITT population (where most patients received VHEC). Using these data, a lower proportion of patients receiving the aprepitant treatment regimen experienced vomiting and rescue medication use compared to the comparator treatment arm. However, due to the lack of relevant MEC data, there is some uncertainty surrounding these results. The company provided an additional scenario analysis whereby the numbers of incomplete responders in both treatment arms were pooled and the average resource use estimated. Based on this analysis the ICER increased to £14,557.
- There is uncertainty surrounding the resource use assumptions used in the economic model. Based on initial SMC expert responses, the assumption that 15% of incomplete responders require hospitalisation in the acute phase appears to be an overestimation. The company provided a revised analysis reducing the proportion to 2.5% (as per the delayed phase) which increased the ICER to £16,925. There was also some uncertainty surrounding the cost per hospitalisation applied in the model. In the base case analysis, the hospitalisation cost was based on paediatric admission for unexplained symptoms with complications and co-morbidities. An additional scenario analysis assuming no complications was requested which increased the ICER to £11,464. A combined analysis was also requested assuming the proportion of incomplete responders in the acute phase requiring hospitalisation was set to 2.5% and the unit cost per hospitalisation was based on no complications, which increased the ICER to £19,709.
- In the base case analysis the time horizon was one treatment cycle. One cycle appears to be appropriate as costs and treatment benefits are likely to remain unchanged over multiple cycles. As an exploratory analysis the company provided three sensitivity analyses whereby the time horizon was increased to 8 treatment cycles and a waning of treatment benefit in both arms of 5%, 10% and 20% per cycle was assumed to apply. Based on these analyses the ICER remained below £2,000.

Despite these issues, the economic case was considered to be demonstrated.

Summary of patient and public involvement

No patient group submission was received.

Additional information: guidelines and protocols

In 2016 the European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) published a guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. It recommends that children receiving MEC should receive anti-emetic prophylaxis with a 5-HT_3 receptor antagonist plus dexamethasone and if they cannot receive dexamethasone they should receive a 5-HT_3 receptor antagonist plus aprepitant.[7]

Additional information: comparators

5HT_3 receptor antagonists with dexamethasone or metoclopramide.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
Aprepitant*	**Orally once daily for three days:** **Children between six months and 12 years: weight-based dose of powder for oral suspension.** **Adolescents (12 to 17 years): one 125mg capsule on day 1 and one 80mg capsule on days 2 and 3.**	**<15kg: 16** **15kg to 30kg: 32** **≥30kg: 47** **47**
Palonosetron**	20 micrograms/kg body weight (up to maximum of 1500 micrograms) as a single 15 minute intravenous infusion beginning approximately 30 minutes before the start of chemotherapy.	Up to 335
Ondansetron**	≤10kg body weight: up to three doses of 0.15mg/kg intravenously at 4-hourly intervals on day 1; then 2mg orally every 12 hours for up to five subsequent days >10kg body weight: up to three doses of 0.15mg/kg intravenously at 4-hourly intervals on day 1; then 4mg orally every 12 hours for up to five subsequent days (total daily dose must not exceed 32mg)	Up to 63 Up to 117
Granisetron** ¥	10 to 40 micrograms/kg body weight (up to maximum of 3mg) by either slow intravenous	Up to 10

	injection or as a diluted intravenous infusion 5 minutes before start of chemotherapy. One additional dose may be administered within a 24 hour-period if required.	

Costs from Dictionary of Medicines and Devices on 04.03.17; cost of aprepitant for children aged <12 years based on body weight and using one sachet for up to three doses.
*Aprepitant is licensed to be administered as part of combination anti-emetic therapy which includes a $5HT_3$ receptor antagonist ± dexamethasone (at 50% of usual oral dose)
**Clinical experts reported use of $5HT_3$ receptor antagonists in combination with dexamethasone (cost per course up to £42) or metoclopramide (cost per course up to £20).
¥Granisetron is contraindicated in children under two years.

Additional information: budget impact

The submitting company estimated there would be 56 patients eligible for treatment with aprepitant in year 1 rising to 57 patients in year 5. The estimated uptake rate was 4% in year 1 (3 patients) rising to 36% in year 5 (21 patients).

The gross impact on the medicines budget was estimated to be £1k in year 1 rising to £8k in year 5. As no medicines were assumed to be displaced, the net medicines budget impact was as per the gross medicines budget impact.

References

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This assessment is based on data submitted by the applicant company up to and including 11 April 2017.

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