

**fosaprepitant, 115mg powder for solution for infusion (Ivemend®)
No. (506/08)**

Merck Sharp & Dohme Limited

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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

fosaprepitant (Ivemend®) is accepted for restricted use within NHS Scotland for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.

Fosaprepitant is marginally more expensive than aprepitant. It is restricted to use in patients for whom aprepitant is indicated but the oral formulation is not appropriate. Prescribing should be initiated by hospital based specialists only.

Fosaprepitant is also licensed for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. As the manufacturer's submission related only to its use with highly emetogenic cancer chemotherapy, SMC cannot recommend its use in this setting.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.

Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Dosing information

Fosaprepitant (115mg) intravenous infusion, administered over 15 minutes, may be substituted for oral aprepitant (125mg) prior to chemotherapy, on day 1 only of the chemotherapy induced nausea and vomiting regimen (containing a corticosteroid and a 5HT₃ antagonist). Fosaprepitant will be followed by aprepitant 80mg daily on days 2 and 3 of the chemotherapy induced nausea and vomiting regimen during each chemotherapy cycle.

Product availability date

1st May 2008

Summary of evidence on comparative efficacy

Fosaprepitant is a water-soluble, phosphorylated prodrug of aprepitant. Following intravenous (IV) administration, it is rapidly distributed to the tissues where it is hydrolysed to aprepitant which is an antagonist of human substance P neurokinin 1 (NK₁) receptors implicated in regulation of the vomiting reflex. The pharmacological activity of fosaprepitant is attributed to aprepitant.

Fosaprepitant is licensed as a possible alternative to oral aprepitant 125mg on day 1 only of the cisplatin-based, cancer chemotherapy induced nausea and vomiting (CINV) regimen. Marketing authorisation for fosaprepitant was granted based on data from the pivotal studies for aprepitant and a fosaprepitant / aprepitant bioequivalence study. Fosaprepitant IV is also licensed for the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy. The manufacturer's submission related to its use in association with highly emetogenic cisplatin-based cancer chemotherapy only.

Bioequivalence study Based on preliminary investigations, fosaprepitant doses of 100mg and 115mg were selected for the definitive investigation of bioequivalence, in terms of aprepitant area under the plasma concentration versus time curve (AUC), to the 125mg licensed oral aprepitant dose.

In an open-label, randomised, 3-period, crossover study, 76 healthy, non-smoking volunteers between 18 and 45 years were randomised to a 15-minute constant rate IV infusion of fosaprepitant 100mg or 115mg, or to oral aprepitant 125mg. There was a 14-day washout interval between treatment periods. Plasma collected for 72 hours was assayed for aprepitant and fosaprepitant.

For approximately four hours post-dose, plasma aprepitant concentrations were higher following fosaprepitant (100mg and 115mg) compared with oral aprepitant (125mg), but were similar between the two treatments thereafter. The maximum plasma aprepitant concentration was approximately 2.5 times higher after fosaprepitant 115mg compared with aprepitant 125mg. At 24 hours post dose, mean plasma aprepitant concentrations were

similar after fosaprepitant 115mg and aprepitant 125mg, but somewhat lower after fosaprepitant 100mg.

Fosaprepitant 115mg IV was AUC bioequivalent to oral aprepitant 125mg; the geometric mean ratio of aprepitant AUC for fosaprepitant 115mg/aprepitant 125mg was 1.13, 90% confidence interval (CI): 1.06 to 1.20. This analysis, based on adjusted data for actual IV dose received, fell within pre-specified equivalence limits of 0.80 to 1.25.

Aprepitant pivotal studies Two multicentre, randomised, parallel group, double blind, placebo-controlled studies evaluated the efficacy of the aprepitant regimen against standard therapy in the prevention of cisplatin-induced nausea and vomiting. The trials recruited cisplatin naïve patients ≥18 years, with a confirmed solid malignancy requiring treatment with a regimen containing cisplatin at a dose ≥70mg/m² on a single day. Patients were required to have a Karnofsky performance score ≥60 (on a scale of 0 to 100 where low scores equate to poor performance status). Additional highly emetogenic chemotherapy was permitted on day 1 only. A modified intention to treat analysis, including all patients who received cisplatin, took study drug and had at least one post-treatment assessment, was used on data for 521 patients (260 in the aprepitant group and 261 in the standard therapy group) and 523 patients (260 in the aprepitant group and 263 in the standard therapy group) in the first and second studies, respectively. In the second study 40 patients from one site were excluded from the efficacy analysis due to unreliable efficacy data.

In both studies the following regimens were used:

- **Aprepitant regimen** - day 1: oral aprepitant 125mg, oral dexamethasone 12mg, IV ondansetron 32mg; days 2 to 3: oral dexamethasone 8mg once daily, oral aprepitant 80mg daily; day 4: oral dexamethasone 8mg once daily.
- **Standard regimen** - day 1: oral dexamethasone 20mg, IV ondansetron 32mg; days 2 to 4: oral dexamethasone 8mg twice daily.

As aprepitant increases dexamethasone levels two-fold, the dexamethasone dose was reduced by approximately 50% in the aprepitant group.

In both studies, there was a statistically significant difference between the aprepitant and standard groups for the primary endpoint of proportion of patients with complete response (no emetic episodes and no rescue therapy) overall (acute and delayed phases); 73% versus 52% and 63% versus 43%, in the first and second studies respectively. The sustainability of the antiemetic effect was investigated by pooling the results of the blinded multiple cycle extensions of each study. This showed that the rate of full emesis protection was significantly higher in the aprepitant group compared with the standard group over multiple chemotherapy cycles.

Summary of evidence on comparative safety

Exposure to fosaprepitant itself is brief (undetectable in the plasma after 30 minutes) as it is rapidly hydrolysed to aprepitant. The European Medicines Agency's European Public Assessment Report (EPAR) states that there are sufficient safety data to support the conclusion that there is acceptable tolerability with the higher aprepitant peak plasma levels that will occur with fosaprepitant relative to oral aprepitant administration.

The two main sources of safety evidence for fosaprepitant are the aggregate aprepitant safety data and the fosaprepitant bioequivalence study. One hundred and twenty-three healthy volunteers received the product under review, 76 of whom received a dose ≥115mg. No data have been provided on the use of the product in the licensed patient population (i.e. patients being treated with highly emetogenic cisplatin-based cancer chemotherapy).

In the pivotal aprepitant studies described earlier, the safety profiles of the aprepitant and standard groups were similar. The overall incidence of clinical adverse events, drug-related clinical adverse events, laboratory adverse events and discontinuation due to clinical adverse events were similar between the treatment groups. Adverse events considered as drug related by the investigator were reported in 17% and 13% of patients in the aprepitant and standard groups respectively. The most common adverse reactions reported at a greater incidence in patients treated with the aprepitant regimen than with standard therapy in patients receiving highly emetogenic chemotherapy were: hiccups (4.6%), asthenia / fatigue (2.9%), ALT increased (2.8%), constipation (2.2%), headache (2.2%) and anorexia (2.0%).

In the bioequivalence study, fosaprepitant was well tolerated at all doses tested and there were no reports of serious adverse events, laboratory adverse events, or discontinuations related to tolerability. Adverse events that did occur with fosaprepitant were mild or moderate in intensity, with headache and infusion site symptoms the most commonly reported. No clinically meaningful relationships were observed for differences between vital signs, physical examinations and ECGs as a function of treatment.

Aprepitant is a substrate, a moderate inhibitor and inducer of cytochrome P450 isoenzyme 3A4 (CYP3A4) and also induces CYP2C9. It has the potential to interact with other drugs as outlined in the Summary of Product Characteristics for fosaprepitant.

Summary of clinical effectiveness issues

There is no evidence for the comparative efficacy of fosaprepitant. The bioequivalence of IV fosaprepitant 115mg to oral aprepitant 125mg has been demonstrated. The EPAR states 'overall from an efficacy perspective, the absence of confirmatory studies is found fully appropriate given the submitted data on pharmacokinetics, available data on the pharmacodynamics of aprepitant and the efficacy results of the Phase III programme of oral aprepitant'.

The EPAR also states that "although higher aprepitant peak levels are observed following fosaprepitant infusion as compared to oral aprepitant, additional efficacy is unlikely, since brainstem NK₁ receptors are already fully occupied with the 125mg oral aprepitant regimen".

Fosaprepitant may be useful in a very small number of patients in whom orally administered medication would not be appropriate prior to initiating chemotherapy, although oral aprepitant would be required on the following two days. However, the CINV prevention regimen used in the aprepitant pivotal studies is not generally used in Scotland. Current clinical guidelines recommend a lower dose of ondansetron than was used in the aprepitant studies and is recommended as part of the licensed fosaprepitant/aprepitant CINV prevention regimen.

Fosaprepitant should be stored in a refrigerator and used immediately after reconstitution and dilution. Preparation and administration of the intravenous infusion requires input from a healthcare professional.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis using a decision tree model with three health states: complete protection, complete response, and incomplete response with continued nausea and vomiting. The time horizon was 5 days: justified as the likely duration of acute and delayed nausea and vomiting associated within the indication. The population of interest was patients for whom aprepitant was indicated but the oral formulation would not be suitable on day one of a three day anti-emetic regimen for the prevention of CINV associated with highly emetogenic cisplatin-based chemotherapy. Two comparisons were presented: one with the trial control arm, and a second with what the manufacturer described as UK practice as derived from expert opinion: ondansetron, dexamethasone and metoclopramide.

The bio-equivalence study was used to justify an assumption that 115mg fosaprepitant would be clinically equivalent to 125mg aprepitant. It was further assumed that the trial control arm would be clinically equivalent to the UK practice comparator.

Quality of life values were drawn from the Visual Analogue Scale results of a study within the literature, though Time Trade Off (TTO) results were apparently also available from the same study. Drug costs were valued using standard references, with the cost of IV administration being based upon it requiring 5 minutes of nursing time. Additional resource use was drawn from the trial and valued using UK sources.

Over the 5-day time horizon, an average patient gain of 0.00172 QALYs was achieved: equivalent to a 0.13 average QoL increment over the treatment period. Based upon the trial comparator arm an additional cost of £39.10 was anticipated, resulting in a cost of £22,784 per QALY. The UK practice based analysis anticipated an additional cost of £21.81, resulting in an estimate of £12,705 per QALY. These estimates reflect the inclusion of an assumed saving of £9.88 from reduced hospitalisation time with the fosaprepitant / aprepitant regimen.

Results were sensitive to the source of utility values, with TTO results roughly doubling the cost effectiveness estimates. The results relative to the trial control arm were also sensitive to the amount of nursing time assumed for an IV administration; allowing up to 20 minutes for this variable increased the cost per QALY by around one third (this did not affect the comparison with UK practice as the same number of IV therapies were required on day one of both regimens). Results were also sensitive to the relatively minor differences in hospitalisation times between the fosaprepitant/aprepitant regimen and the comparators. Equalising these also increased the cost per QALY by around one third.

Despite these issues the manufacturer presented a sufficiently robust economic case to gain acceptance by the SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Multinational Association of Supportive Care in Cancer (MASCC) guidelines, updated in 2008, state that to prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5HT₃ antagonist, dexamethasone and aprepitant (or fosaprepitant) given before chemotherapy is recommended.

The National Comprehensive Cancer Network (NCCN) antiemesis guidelines, published in 2008, include aprepitant and fosaprepitant as part of standard antiemetic therapy for patients receiving highly emetogenic chemotherapy. Fosaprepitant 115mg may be substituted for aprepitant 125mg 30 minutes prior to chemotherapy on day 1 only of the CINV regimen.

The American Society of Clinical Oncology (ASCO) guidelines, updated and published in 2006, predate the fosaprepitant licence. They recommend the three-drug combination of a 5HT₃ antagonist, dexamethasone and aprepitant before chemotherapy of high emetic risk.

Additional information: previous SMC advice

Following a full submission, SMC published advice in February 2006: aprepitant 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.

Following a full submission, SMC published advice in November 2004: aprepitant is accepted for restricted use within NHS Scotland for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy. The antiemetic regimen incorporating aprepitant was superior to one regimen (where dexamethasone alone was used in the delayed phase of treatment), for the prevention of cisplatin-induced nausea and vomiting in the acute and delayed phases. It should be initiated only by appropriate hospital based specialists.

Following a full submission, SMC published advice in November 2005: palonosetron (Aloxi[®]) is accepted 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. It is as effective as other 5HT₃ antagonists in preventing emesis when given as a single intravenous injection following highly emetogenic chemotherapy (HEC) in the acute phase and moderately emetogenic chemotherapy (MEC) in the acute and delayed phases post-chemotherapy.

Additional information: comparators

Fosaprepitant 115mg intravenous infusion is licensed as a possible alternative to oral aprepitant 125mg on day 1 only of the CINV regimen. There are no other licensed NK₁ receptor antagonists.

Cost of relevant comparators

Regimen	Doses	Cost per cycle (£)
fosaprepitant followed by aprepitant	115mg fosaprepitant (IV infusion) on day 1 of antiemetic regimen followed by 80mg oral aprepitant daily on days 2 and 3	52.16 ^a
aprepitant	125mg aprepitant (orally) on day 1 of antiemetic regimen followed by 80mg oral aprepitant daily on days 2 and 3	47.42 ^b

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS, June 2008. a) Cost calculation assumes that 1 vial of 115mg fosaprepitant costing £20.55 was used on day 1, followed by the use of the 2 day pack of 80mg aprepitant (£31.61). b) Cost calculation assumes the use of the three day pack of aprepitant that contains 1 x 125mg and 2 x 80mg capsules (£47.42).

Additional information: budget impact

The manufacturer estimated a gross drug cost for fosaprepitant coupled with aprepitant of £2,000 in year 1, rising to £2,400 by year 5. This assumed the prevention of emesis associated with 38 cycles of chemotherapy in year 1, rising to 46 by year 5, . The net drug cost of the fosaprepitant / aprepitant regimen was estimated as being £1,400 in year 1, rising to £1,700 by year 5, due to offset savings from reduced use of ondansetron, dexamethasone and metoclopramide.

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 25 July 2008.

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. The reference shaded grey is additional to those supplied with the submission.

Lasseter KC, Gambale J, Jin B et al. Tolerability of fosaprepitant and bioequivalency to aprepitant in healthy subjects. *J Clin Pharmacol* 2007 Jul;47(7):834-40.

Hesketh PJ, Grunberg SM, Gralla RJ et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin - The Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003;21(22):4112-19.

Poli-Bigelli S, Rodrigues-Pereira J, Carides AD et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003;97(12):3090-8.

De Wit R, Herrstedt J, Rapoport, B et al. The oral NK₁ antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. *Eur J Cancer* 2004;40(3):403-10.

European Medicines Agency (EMA). European Public Assessment Report (EPAR) for fosaprepitant. (www.emea.eu.int)