

Aprepitant

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Aprepitant is an oral antiemetic licensed to be combined with existing regimens to prevent both acute and delayed high dose cisplatin-induced nausea and vomiting, which patients find very distressing. As a substance P antagonist it has a novel mode of action.
- When combined with a fixed cisplatin antiemetic regimen of ondansetron (on day 1 only) and dexamethasone, aprepitant reduced acute and delayed emesis compared to the fixed regimen alone. The aprepitant regimen did not eliminate emesis in all patients, but it was significantly superior in two phase III trials involving over one thousand patients.
- The relevance of these results is of concern as aprepitant was compared neither to a standard American Society of Clinical Oncology (ASCO) antiemetic regimen nor to a common UK regimen. The effects of aprepitant on nausea and vomiting induced by other, less emetogenic chemotherapy agents is unknown.
- Aprepitant appears well tolerated, but it may interact with a range of drugs, including dexamethasone and common chemotherapy agents. Care with patient selection is therefore required.
- Aprepitant costs £47.42 per cycle of cisplatin based chemotherapy.

Introduction

Cisplatin-induced nausea and vomiting is particularly distressing and affects most patients given the drug. Acute nausea and vomiting (N&V) occurs during the first 24 hours after receiving it, and delayed N&V occurs over the ensuing 2-5 days.

Serotonin (5HT) mediates acute emesis due to chemotherapy, so the use of a 5HT₃ receptor antagonist to prevent it is an established approach.¹ However, substance P may have a more central role in mediating vomiting due to many causes, including delayed emesis.² Aprepitant is a substance P antagonist, acting at neurokinin-1 receptors.^{3,4}

Evidence

Aprepitant has been studied in five phase II clinical trials⁵⁻⁹ and two phase III trials.^{10,11} None of the phase II trials involved the licensed dose regimen, but they did show that aprepitant is more effective when added to an ondansetron/ dexamethasone regimen than when given alone. There was also shown to be no value in giving aprepitant the day before cisplatin.

The two phase III randomised, double-blind, placebo-controlled trials each recruited over 500 cisplatin-naïve patients who were due to receive cisplatin at a dose $\geq 70\text{mg/m}^2$ (mean dose used approximately 81mg/m^2)^{10,11}. In both trials patients received one of two regimens:

- Group 1: i.v. ondansetron 32mg + oral dexamethasone 20mg on day 1 (the day of cisplatin therapy), followed by oral dexamethasone 8mg twice a day on days 2-4.
- Group 2: oral aprepitant 125mg + i.v. ondansetron 32mg + oral dexamethasone 12mg on day 1; then oral aprepitant 80mg once daily on days 2-3 plus oral dexamethasone 8mg once daily on days 2-4.

Brand Name, (Manufacturer): Emend, (MSD).

Licensed Indications: Prevention of cisplatin induced nausea and vomiting in adults, when given with dexamethasone and a 5HT₃ antagonist.

Dosage: 125mg orally (day 1), then 80mg (days 2 and 3).

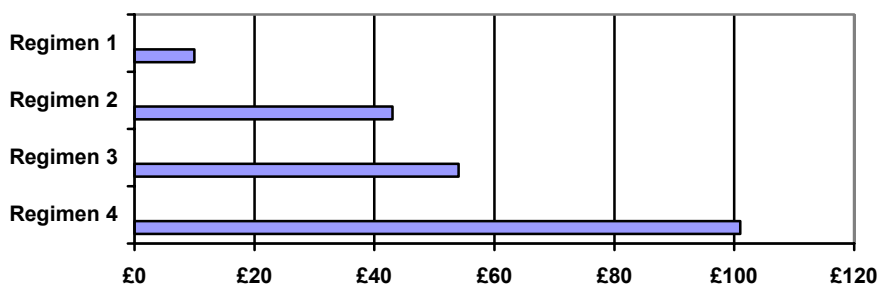
Cost Comparison [MIMS & Drug Tariff March 2004].

Regimen 1: A common existing UK regimen: Ondansetron 8mg oral + dexamethasone 8mg oral (day 1). Then oral dexamethasone 2mg tds for 3 days + oral metoclopramide 10-20mg tds prn for 4 days.

Regimen 2: A current ASCO recommended regimen¹: Ondansetron 8mg i.v. + dexamethasone 20mg i.v. (day 1). Then oral dexamethasone 8mg bd for 3-4 days plus oral ondansetron 8mg od for 2-3 days.

Regimen 3: Phase III trials comparator regimen: Ondansetron 32mg i.v. + oral dexamethasone 20mg (day 1). Then dexamethasone 8mg bd (days 2-4).

Regimen 4: Phase III trials aprepitant regimen: Aprepitant 125mg + ondansetron 32mg i.v. + oral dexamethasone 12mg. Then aprepitant 80mg od (days 2-3) + oral dexamethasone 8mg od (days 2-4).



N.B. Regimens shown for general comparison and do not imply therapeutic equivalence

Aprepitant

In aprepitant recipients, steroid doses were halved, since aprepitant doubles dexamethasone levels. The primary endpoint in both trials was the proportion of patients with complete response (no emetic episodes & no rescue medication).

In both trials, the proportion of patients with complete response was significantly greater in the aprepitant groups throughout the 5-day study period (62.7% vs. 43.3%, $p < 0.001$ ¹⁰ and 72.7% vs. 52.3%, $p < 0.001$ ¹¹). For acute emesis and delayed emesis complete response was significantly greater in the aprepitant groups (**Table 1**).

Quality of life, as assessed by the Functional Living Index – Emesis (FLIE) questionnaire, was improved in aprepitant recipients compared to non-recipients in both trials.¹⁰⁻¹²

The effect of aprepitant in multiple cycles of cisplatin chemotherapy was assessed from extended phase III trials.¹³ The endpoint was no emesis and no significant nausea. In each cycle the estimated probabilities of the end point stayed significantly higher in the aprepitant group ($p \leq 0.006$):

- 61% in cycle 1 [n=516] & 59% by cycle 6 [n=89] for aprepitant.
- 46% in cycle 1 [n=522] & 40% by cycle 6 [n=78] for the non-aprepitant group.

Another study (n=202) found higher estimated probabilities of a complete response maintained through up to six cisplatin cycles in aprepitant recipients, compared with groups not given aprepitant.¹⁴ However, patients in this study received aprepitant for a full five days, which is unlicensed. Although the advantages of aprepitant were maintained across cycles in these two studies, the number of patients available for assessment declined in successive cycles.^{13,14}

Safety⁴

Side effects are generally minor. The major safety issue is interactions. Aprepitant is contra-indicated in patients receiving some drugs (e.g. terfenadine,

pimozide). It is metabolised by CYP3A4, so drugs which inhibit the enzyme (e.g. itraconazole) may increase aprepitant levels. Aprepitant also inhibits CYP 3A4. Chemotherapy drugs metabolised by CYP 3A4 may need dose reduction – e.g. dexamethasone, taxanes, vinca alkaloids, etoposide, ifosfamide and irinotecan. It is recommended that dexamethasone doses are halved in aprepitant recipients.

Aprepitant also induces CYP2C9 so it may decrease the efficacy of drugs such as warfarin & phenytoin.

Place in Therapy

Points for consideration:

- Aprepitant has demonstrated efficacy against cisplatin induced N&V, as combination to one specific ondansetron/dexamethasone regimen. This regimen is suggested for use in the SPC⁴ and it is expensive. The regimen does not reflect current UK antiemetic practice or ASCO recommendations.¹
- Aprepitant is a prophylactic drug – it has not been investigated as a treatment for established N&V.
- In clinical trials, aprepitant was given to cisplatin naïve patients. Anticipatory vomiting could frustrate attempts to limit aprepitant to cisplatin recipients who have already failed other options since once an emetic response is established it can be more difficult to control.
- The phase III trials recruited patients receiving high doses of cisplatin – it is not known how effective aprepitant would be in patients receiving lower doses.
- There are no data to support use of aprepitant for preventing N&V caused by less emetogenic chemotherapy than cisplatin.
- Aprepitant has not been studied in non-chemotherapy causes of acute vomiting (eg post-operative).
- No pharmacoeconomic studies are available.

The Future

Investigation as a treatment for other causes of N&V must be anticipated. Aprepitant is also in phase II trials as an anxiolytic.

Key Papers

10. Poli-Bigelli S 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: 3090-8.

11. Hesketh PJ 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: 4112-9.

13. De Wit R 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: 403-10.

14. De Wit R et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *J Clin Oncol* 2003;21: 4105-11.

Appendix I: Bibliography

Appendix II: Table of Clinical Trials

Risk Management Issues:

None noted



Adapted from the "On the Horizon-Future Medicines" produced by a collaboration between the NPC and the Wessex Drug & Medicines Information Centre.

Produced for the UK Medicines Information Service
by Dr Simon Wills, Wessex Drug & Medicines Information Centre, Southampton. Tel 023 8079 6908.

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Appendix I

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11. 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: 4112-9.
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Aprepitant

Appendix II

Table 1: Phase III Clinical Trials of Aprepitant for Preventing Cisplatin-induced Nausea and Vomiting

Ref	Trial Design	Trial Population	Treatment	Primary Outcomes
10	Randomised, double-blind, placebo-controlled, multicentre trial in South America.	569 adult cisplatin naïve patients with cancer, receiving at least 70mg/m ² cisplatin. Note only 523 patients were evaluated for efficacy. This was mainly due to one study site where efficacy data for 40 patients were considered unreliable after an audit, and withdrawn.	Group 1: i.v. ondansetron 32mg + oral dexamethasone 20mg on day 1. Then oral dexamethasone 8mg bd for days 2 – 4. Group 2: oral aprepitant 125mg + i.v. ondansetron 32mg + oral dexamethasone 12mg on day 1. Then oral aprepitant 80mg od for days 2 – 3 + oral dexamethasone 8mg od for days 2 – 4.	Response for the primary efficacy endpoint of complete response (no emesis and no rescue therapy): Days 1-5 (overall study period): Grp 1 = 43.3%; Grp 2 = 62.7%; p<0.001 Response for some secondary/exploratory efficacy endpoints: Complete response Day 1 (acute emesis): Grp 1 = 68.4%; Grp 2 = 82.8%; p<0.001 Complete response Days 2-5 (delayed emesis): Grp 1 = 46.8%; Grp 2 = 67.7%; p<0.001 Complete protection Days 1-5: Grp 1 = 41%; Grp 2 = 56%; p<0.01 (no emesis, no rescue therapy, no significant nausea) Total control Days 1-5: Grp 1 = 32%; Grp 2 = 44%; p<0.01 (no emesis, no rescue therapy, no nausea) No significant nausea Days 1-5: Grp 1 = 64%; Grp 2 = 71%; p=NS
11	Randomised, double-blind, placebo-controlled, multicentre international trial, including Europe.	521 adult cisplatin naïve patients with cancer, receiving at least 70mg/m ² cisplatin.	Group 1: i.v. ondansetron 32mg + oral dexamethasone 20mg on day 1. Then oral dexamethasone 8mg bd for days 2 – 4. Group 2: oral aprepitant 125mg + i.v. ondansetron 32mg + oral dexamethasone 12mg on day 1. Then oral aprepitant 80mg od for days 2 – 3 + oral dexamethasone 8mg od for days 2 – 4.	Response for the primary efficacy endpoint of complete response (no emesis and no rescue therapy): Days 1-5 (overall study period): Grp 1 = 52.3%; Grp 2 = 72.7%; p<0.001 Response for some secondary/exploratory efficacy endpoints: Complete response Day 1 (acute emesis): Grp 1 = 78.1%; Grp 2 = 89.2%; p<0.001 Complete response Days 2-5 (delayed emesis): Grp 1 = 55.8%; Grp 2 = 75.4%; p<0.001 Complete protection Days 1-5: Grp 1 = 49%; Grp 2 = 63%; p<0.01 (no emesis, no rescue therapy, no significant nausea) Total control Days 1-5: Grp 1 = 40%; Grp 2 = 46%; p=NS (no emesis, no rescue therapy, no nausea) No significant nausea Days 1-5: Grp 1 = 66%; Grp 2 = 73%; p=NS

NS = Not significant