

Drug Review: Fosaprepitant

Abstract

Chemotherapy-induced nausea and vomiting (CINV) is a significant contributor to the treatment morbidity experienced by patients with cancer. With effective prophylactic anti-emetics given prior to administration of moderately or highly emetogenic chemotherapy (MEC or HEC) it is expected that 70-80% of patients will have no CINV. Fosaprepitant is an intravenous prodrug of aprepitant that acts as an anti-emetic by blocking the neurokinin (NK-1) receptor. Fosaprepitant in combination with dexamethasone and 5-HT₃ antagonist like ondansetron has been shown to be effective in preventing CINV in patients receiving MEC or HEC. The current review discusses the pharmacology and clinical indications for the use of fosaprepitant. The evidence for the effectiveness of fosaprepitant in the prevention of CINV and the commonly observed adverse events with its administration is discussed in this review.

Keywords: Chemotherapy, fosaprepitant and NK1 antagonist, vomiting

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is the most common debilitating side effect of chemotherapy administration.^[1-3] It affects 50%–80% of adult and pediatric patients receiving moderate to highly emetogenic chemotherapy (MEC or HEC).^[1-3] The National Comprehensive Cancer Network (NCCN) 4-point scale and the 4-point pediatric scale proposed by Dupuis *et al.* are used for classifying the emetogenicity of chemotherapy drugs without the use of prophylactic antiemetics.^[4,5] According to the scales, agents with a predicted incidence of CINV <10% are graded as minimal-risk emetogenic potential, 10%–30% as low-risk, 30%–90% as moderate-risk, and >90% as high-risk emetogenic potential.^[4,5]

Acute CINV is defined as CINV occurring within 24 h of administration of the last dose of chemotherapy and delayed as CINV occurring 24 h after and till 5 days from the last dose of chemotherapy. Chemotherapeutic agents cause nausea and vomiting by acting on peripheral and central receptors. Acute CINV is mediated by 5-hydroxytryptamine (5-HT₃) receptors located in the enterochromaffin cells of

the gut.^[6] Delayed CINV is predominantly driven by a central pathway involving the neurokinin-1 (NK-1) receptor; therefore, the addition of an NK-1 receptor antagonist like fosaprepitant to antiemetic prophylactic regimens involving a 5-HT₃ receptor antagonist and a corticosteroid has been found to be most useful in preventing delayed CINV.^[7] Substance-P is the most important activator of the NK-1 receptor.^[7]

Fosaprepitant was approved by the United States of America Food and Drug Administration (FDA) in 2008 for use as a prophylactic antiemetic for preventing CINV in patients receiving MEC or HEC in combination with a 5-HT₃ antagonist and dexamethasone. The current drug update will focus on the pharmacology and clinical aspects of the use of fosaprepitant in oncology.

Mechanism of Action

Fosaprepitant is a prodrug of aprepitant, and its actions are attributable to aprepitant. Aprepitant is a highly selective antagonist of substance-P/NK-1 receptor. After administration, fosaprepitant is rapidly converted in the blood, liver, kidney, and ileum to aprepitant.^[8] Plasma levels of fosaprepitant are below the level of detection (10 ng/mL) within 30 min after its infusion.^[8] Aprepitant is primarily metabolized CYP3A4 enzyme in the liver and other tissues.^[8] It is excreted in the

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urine and stools and has a half-life of 9–13 h.^[8] Aprepitant is 95% protein bound.

Indication for Use

The FDA has approved the use of fosaprepitant for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and delayed nausea and vomiting associated with initial and repeat courses of MEC in adults and children above 6 months of age.^[9,10] The Central Drugs Standard Control Organization of India has approved the use of fosaprepitant for the above indications in adults.

Dosage form and strength

150 mg, lyophilized powder in a single-dose vial for reconstitution.

Dose and administration

The dose and schedule for administration of fosaprepitant in adults have been given in Table 1 and for children in Tables 2 and 3.^[9,10]

Fosaprepitant is administered in 150 ml normal saline (145 ml normal saline + 5 ml fosaprepitant). The final concentration before administration should be 1 mg/ml. Fosaprepitant is incompatible with any solutions containing divalent cations (e.g., Ca²⁺, Mg²⁺), including Lactated Ringer's Solution and Hartmann's Solution. The reconstituted final drug solution is stable for 24 h at ambient room temperature (at or below 25°C).^[9,10]

Drug Interactions

Fosaprepitant is an inhibitor of the CYP3A4 enzyme in the liver and increases the serum level of many drugs metabolized by CYP3A4.^[11] It is recommended to reduce dexamethasone dose by 50% for the first 48 h after administration of fosaprepitant as it has been shown that the dexamethasone levels increase after administration of aprepitant or fosaprepitant.^[12] The recent NCCN guidelines for adults have a reduced dexamethasone dose of 12 mg on day 1 and 8 mg once a day on day 2–4 of chemotherapy administration. Therefore, guidelines do not recommend further dose reduction of dexamethasone when administered

Table 1: Fosaprepitant administration schedule for adults (>18 years) for highly or moderately emetogenic chemotherapy

	Day 1	Day 2	Day 3	Day 4
Fosaprepitant	150 mg intravenously over 20-30 min approximately 30 min before chemotherapy	None	None	None
Dexamethasone	12 mg orally	8 mg orally	8 mg orally	8 mg orally*
5HT3 antagonist	Dose and duration according to the drug used	-	-	-

*Dexamethasone only on day 2 and 3 for MEC. MEC – Moderate to highly emetogenic chemotherapy; 5HT – 5-hydroxytryptamine

Table 2: Fosaprepitant administration schedule for children receiving single-day highly or moderately emetogenic chemotherapy

	Age	Regimen
Fosaprepitant	>12 years	150 mg intravenously over 30 min
	2 years-<12	4 mg/kg (maximum dose 150 mg) intravenously over 60 min
	6 months-<2 years	5 mg/kg (maximum dose 150 mg) intravenously over 60 min
Dexamethasone	6 months-17 years	If a corticosteroid, such as dexamethasone, is coadministered, administer 50% of the recommended corticosteroid dose on days 1 and 2
5HT3 antagonist	6 months-17 years	Dose according to the drug used

5HT – 5-hydroxytryptamine

Table 3: Fosaprepitant administration schedule for children receiving multiday highly or moderately emetogenic chemotherapy

Age group	Drug	Day 1	Day 2	Day 3*
12-17 years	Fosaprepitant	115 mg intravenously over 30 min	-	-
	Aprepitant		80 mg orally	80 mg orally
6 months-<12 years	Fosaprepitant	3 mg/kg (maximum dose 115 mg) intravenously over 60 min	-	-
	Aprepitant oral suspension ⁺		2 mg/kg orally (maximum 80 mg)	2 mg/kg orally (maximum 80 mg)
6 months-17 years	Dexamethasone	If a corticosteroid, such as dexamethasone, is coadministered, administer 50% of the recommended corticosteroid dose on days 1 through 4		
6 months-17 years	5HT3 antagonist	Dose and duration according to the drug used		

*Dexamethasone should be continued for 48 h after the last dose of chemotherapy. ⁺Aprepitant pediatric formulations are currently not available in India, and the adult dose capsules are approved for use in children above the age of 12 years. 5HT – 5-hydroxytryptamine

with aprepitant or fosaprepitant.^[4] Pediatric guidelines recommend a dexamethasone dose of 16–24 mg/m², which is higher compared to doses recommended in adults, and therefore, pediatric patients receiving dexamethasone should have their dose reduced by 50% for the first 48 h after administration of fosaprepitant.^[13]

There are concerns that aprepitant and fosaprepitant by inhibiting the CYP3A4 enzyme can increase the serum levels and thereby the adverse effects of chemotherapy drugs such as cyclophosphamide, ifosfamide, vinblastine, and vincristine that are CYP3A4 substrates.^[11] However, randomized trials with aprepitant and fosaprepitant in children and adults included the above drugs and did not show any concerning adverse effects.^[14-17] The FDA recommends close monitoring for adverse effects when fosaprepitant is used concomitantly with chemotherapeutic agents that have significant interactions.

Coadministration of fosaprepitant with warfarin can decrease the prothrombin time, and therefore, frequent monitoring of international normalized ratio is required.^[9,10] Fosaprepitant reduces the efficacy of oral contraceptive pills (OCPs), and therefore, other methods of contraception should be advised to patients on OCPs receiving fosaprepitant.^[9,10]

Adverse Reactions

Fosaprepitant is a safe drug with minimal side effects reported in randomized trials.^[14-17] Infusion site reactions such as pain, irritation, and thrombophlebitis were more common with fosaprepitant when compared to standard therapy (2.2% vs. 0.6%).^[15] These reactions were more common in patients receiving vesicant drugs such as anthracyclines. The FDA recommends that fosaprepitant should be given through a central line in children. However, a recent randomized trial in children showed that it is safe to administer fosaprepitant through a peripheral line without increased incidence of thrombophlebitis.^[10,17]

Use in Special Circumstances

The effect of fosaprepitant in pregnancy and lactation has not been studied. Although animal studies have shown that fosaprepitant is safe in pregnancy,^[9,10] no dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child–Pugh score 5–9) and renal impairment.^[9,10] There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child–Pugh score >9), and therefore, close clinical monitoring is required in this group of patients.^[9,10]

Clinical Efficacy

In a Phase III, double-blind trial, adult cancer patients scheduled to receive MEC, a single-dose fosaprepitant 150 mg was compared to placebo. Both arms received ondansetron and dexamethasone on day 1. Complete

response (CR) rate was defined as no vomiting or use of rescue medications. The fosaprepitant regimen improved the CR rate significantly in the delayed (78.9% vs. 68.5%; $P < 0.001$) and overall (77.1% vs. 66.9%; $P < 0.001$) phases, but not in the acute phase (93.2% vs. 91.0%; $P = 0.184$), versus placebo.^[14]

A randomized, double-blind, noninferiority clinical trial with 2322 patients receiving cisplatin ≥ 70 mg/m² compared a 3-day oral aprepitant schedule to a regimen containing a single dose of intravenous fosaprepitant.^[15] All patients received dexamethasone and ondansetron prophylaxis. The trial showed that fosaprepitant was noninferior to aprepitant with regard to CR rates.^[15] The only increased adverse event noticed with fosaprepitant in comparison to aprepitant was thrombophlebitis.

Fosaprepitant has been found to be effective when administered weekly with palonosetron and dexamethasone in patients with cervical cancer receiving weekly cisplatin concurrent with radiotherapy. The proportion of patients with sustained no emesis at 5 weeks in the trial was 48.7% for the placebo group compared with 65.7% for patients in the fosaprepitant group.^[16]

FDA approved the use of fosaprepitant in children above 6 months of age in May 2018. However, this approval was based on unpublished data submitted by Merck pharmaceuticals to FDA. The only randomized controlled trial till date on the use of fosaprepitant in children was published by Radhakrishnan *et al.* in November 2018.^[17] The study randomized 163 pediatric patients between the age of 1 and 12 years receiving MEC or HEC to fosaprepitant and placebo. Both arms received dexamethasone and ondansetron. CR rates defined as no vomiting were significantly higher in the fosaprepitant arm compared to those in the placebo arm during the acute phase of vomiting (86% vs. 60%, $P < 0.001$), delayed phase (79% vs. 51%, $P < 0.001$), and overall phase (70% vs. 41%, $P < 0.001$). This trial used a fosaprepitant dose of 3 mg/kg (maximum 150 mg) administered over 30 min like the adult schedule rather than the FDA recommended dose of 4 mg/kg in children between 2 and 12 years and 5 mg/kg in children between 6 months and 2 years administered over 60 min.^[10,17] FDA recommends a higher dose and longer duration of fosaprepitant administration in children compared to adults because pharmacokinetic data have shown that children <12 years convert fosaprepitant to aprepitant in the blood slowly compared to adults and achieve a lower mean area under the curve.^[10] Despite using a reduced dose and shorter infusion time, no reduction in efficacy or increase in adverse events were noted in the study by Radhakrishnan *et al.*^[17]

Conclusion

Fosaprepitant is a prodrug of aprepitant that is safe, easy to administer, and requires only a single-dose administration

unlike a 3-day course of oral aprepitant, thereby, increasing patient compliance. It has been shown in randomized controlled trials to be effective and noninferior to aprepitant in preventing CINV due to MEC and HEC.

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Conflicts of interest

There are no conflicts of interest.

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