6.1 Clinical Trials Experience

Infusion site reactions (ISRs) have been reported with the use of fosaprepitant for injection. Reactions have been particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle.

Coadministration of fosaprepitant with warfarin, a CYP2C9 substrate, may result in a clinically significant increase in warfarin plasma concentrations and decreased efficacy of fosaprepitant.

Severe ISRs consisted of medical, and in some cases surgical, intervention.

5.2 Clotrimazole

Clotrimazole is a substrate, inhibitor, and inducer of CYP3A4.

Infusion of dextrose 5% in water in a plastic bag every 24 hours at a rate of 100 mL/hour for 5 consecutive days.

In vitro and clinical studies indicate inhibited fosaprepitant plasma concentrations and decreased efficacy of fosaprepitant. Concomitant use with strong or moderate CYP3A4 inhibitors (e.g., ketoconazole, erythromycin) should be avoided.

Use of Fosaprepitant with strong or moderate CYP3A4 inhibitors (e.g., ketoconazole, erythromycin) may result in a reduction in fosaprepitant plasma concentrations and decreased efficacy of fosaprepitant.

Use of Fosaprepitant with strong CYP3A4 inducers (e.g., rifampin) may result in a reduction in fosaprepitant plasma concentrations.

Combination therapy with irinotecan and strong CYP3A4 inducers (e.g., rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of aprepitant.

Infusion of dextrose 5% in water in a plastic bag every 24 hours at a rate of 100 mL/hour for 5 consecutive days.

Anaphylactic reactions, flushing, erythema, and dyspnea have been reported. Use of fosaprepitant for injection has not been studied for the treatment of established nausea and vomiting.

Clinically Significant CYP3A4 Drug Interactions

See selected 5-HT3 receptor antagonist prescribing information.

3. DOSAGE AND ADMINISTRATION

Recommended Dosing for the Prevention of Nausea and Vomiting Associated with Highly Emotionogenic Chemotherapy (HEC)

Most common adverse reactions in adults (≥2%) are: fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral edema, headache, rash, and postural hypotension.

Administer fosaprepitant for injection as an intravenous infusion; complete the infusion approximately 30 minutes prior to chemotherapy.

Adults: 150 mg on Day 1.

Step 1. Reconstitute 5 mL of fosaprepitant for injection (50 mg/mL) with 50 mL of sterile water for injection, resulting in a final concentration of 1 mg/mL.

Step 2. Transfer the reconstituted drug solution to a glass vial for reconstitution.

Step 5. Infuse the reconstituted fosaprepitant for injection over approximately 30 minutes. Administer fosaprepitant for injection at a rate of 0.004 mg/mL/hour.

Step 6. Use a single-use, stop-flow, in-line filter (0.2 micron) compatible with intravenous administration before infusion.

Step 7. Administer fosaprepitant for injection at a rate of 0.004 mg/mL/hour, as a single dose.

13.1 Carcinogenesis, Mutagenesis, Impairment Of Fertility

No evidence of carcinogenic activity was observed in mice and rats treated with fosaprepitant for injection at doses up to 50 and 10 mg/kg/day, respectively, in the presence or absence of food.

No evidence of increased genotoxic potential of fosaprepitant for injection in mouse bone marrow micronucleus assay.

Fosaprepitant for injection did not impair the fertility of rats at doses of up to 10 mg/kg/day, which is up to 5 times (based on AUC) the human systemic exposure at the maximum recommended dose.

5.6 Monitoring of Laboratory Tests

A routine laboratory test battery is sufficient for monitoring and assessing the effects of fosaprepitant for injection. Additional laboratory tests may be appropriate for patients with underlying diseases.
The safety and effectiveness of fosaprepitant dimeglumine for the prevention of nausea and vomiting associated with MEC in patients aged 65 years and over have not been studied. In studies of patients 65 years of age and older, the most common adverse reactions were constipation (12.3%), diarrhea (12.3%), dizziness (12.3%), pruritus (12.3%), headache (12.3%), dyspepsia (12.3%), urticaria (12.3%), urticaria (12.3%), and pruritus (12.3%). The incidence of pruritus, rash, and urticaria in the fosaprepitant group was greater than that in the aprepitant group (12.3%, 12.3%, and 12.3%, respectively). Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug product cannot be directly compared to rates observed in clinical trials of another drug product and may not reflect the rates observed in practice.

In embryofetal development studies in rats and rabbits, aprepitant was administered during the period of organogenesis. In a toxicology study in juvenile dogs treated with fosaprepitant from postnatal day 14 (equivalent to a human weight of approximately 15 kg), no evidence of adverse effects in growth and development was observed. However, a limited number of rats and rabbits treated with fosaprepitant at a high dose (40 mg/kg/day) showed signs of maternal toxicity and poor fetal outcomes, such as a high incidence of resorptions and stillbirths. In a study in young rats, fosaprepitant was administered from postnatal day 10 to weaning. Neurobehavioral tests of sensory function, motor function, and learning and memory were conducted. Although certain behavioral measures were altered at the highest dose of fosaprepitant (40 mg/kg/day), the results were not considered to be evidence of adverse effects. In a study in adult rabbits, fosaprepitant was administered at doses of 20, 50, 150, and 400 mg/kg/day. In this study, the uterus and cervix, and edema of vaginal tissues were seen in females from 4 mg/kg/day. A study was also conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and learning and memory functions. Aprepitant was administered to rats from weaning to adulthood, and the effects on growth and development were assessed. No significant differences in growth or development were observed in the aprepitant group compared to the vehicle group.

In a toxicity study in juvenile dogs treated with fosaprepitant from postnatal day 14 (equivalent to a human weight of approximately 15 kg), no evidence of adverse effects in growth and development was observed. However, a limited number of rats and rabbits treated with fosaprepitant at a high dose (40 mg/kg/day) showed signs of maternal toxicity and poor fetal outcomes, such as a high incidence of resorptions and stillbirths. In a study in young rats, fosaprepitant was administered from postnatal day 10 to weaning. Neurobehavioral tests of sensory function, motor function, and learning and memory were conducted. Although certain behavioral measures were altered at the highest dose of fosaprepitant (40 mg/kg/day), the results were not considered to be evidence of adverse effects. In a study in adult rabbits, fosaprepitant was administered at doses of 20, 50, 150, and 400 mg/kg/day. In this study, the uterus and cervix, and edema of vaginal tissues were seen in females from 4 mg/kg/day. A study was also conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and learning and memory functions. Aprepitant was administered to rats from weaning to adulthood, and the effects on growth and development were assessed. No significant differences in growth or development were observed in the aprepitant group compared to the vehicle group.

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The efficacy of fosaprepitant for injection was evaluated based on the primary and pre-specified secondary endpoints. The non-inferiority margin for no vomiting in the overall phase was 8.2% and for complete response in the overall phase was 7%. The pre-specified non-inferiority margin for an overall effect was 9%.

**Overall Endpoints**

- **Complete Response:** Fosaprepitant showed non-inferiority to Ondansetron based on the primary endpoint of complete response. The non-inferiority margin was 7%.
- **Delayed Phase:** Fosaprepitant also demonstrated non-inferiority in the delayed phase, with a margin of 9%.

**SECONDARY ENDPOINTS**

- **Incidence of Emesis:** Fosaprepitant showed a lower incidence of emesis compared to Ondansetron, with a difference of 9% in the overall phase and 10% in the delayed phase.
- **Induction Phase:** Similar to the overall phase, the incidence of emesis was lower with fosaprepitant, with a difference of 9%.

**Pharmacokinetics**

- **Single 150-mg Oral Dose:** Following a single 150-mg oral dose of fosaprepitant, the mean terminal half-life of fosaprepitant was approximately 2.7 hours and the mean AUC was 10.5 mcg·h/mL. The terminal half-life of aprepitant was approximately 10 hours.
- **Multiple Dose Administration:** When administered as a multiple dose regimen, fosaprepitant showed linear pharmacokinetics.

**Safety and Tolerability**

- **Adverse Events:** The most commonly reported adverse events were mild to moderate in severity and were generally consistent with those observed with other antiemetic agents.
- **Drug Interactions:** Fosaprepitant does not affect the QTc interval in healthy volunteers.

**Conclusion**

Fosaprepitant for injection is an effective antiemetic agent that demonstrates non-inferiority to Ondansetron based on the primary and secondary endpoints. It is well tolerated and has a favorable safety profile.
Fosaprepitant for Injection

Table 14 Percent of Adult Patients Receiving MEC Responding by Treatment Group

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Complete Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Ondansetron</td>
<td>55.7 (9.8, 71.8)</td>
</tr>
<tr>
<td>Fosaprepitant Regimen</td>
<td>68.5 (5.7, 85.3)</td>
</tr>
<tr>
<td>Standard Therapy</td>
<td>4.4 (3.0, 5.8)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>5.8 (5.1, 6.6)</td>
</tr>
<tr>
<td><strong>N: Number of Patients Included</strong></td>
<td>1,000</td>
</tr>
</tbody>
</table>

Complete Response = no vomiting and no use of rescue therapy.

**Table Legend:**
- **N**: Number of patients included in the primary analysis of complete response.
- **95% CI**: 95% confidence interval.
- **Primary Endpoint**: MEC on Day 1 and the second dose was administered 8 hours after first ondansetron dose.
- **Delayed Phase Endpoint**: MEC on Day 1 and the second dose was administered 8 hours after first ondansetron dose.
- **Analysis Model**: Miettinen and Nurminen.
- **Analysis**: Adjusted for Gender.
- **Primary Endpoint (MEC)**: Overall response on Day 1 and the second dose was administered 8 hours after first ondansetron dose.

**Analysis Model:**
- **Analysis**: Miettinen and Nurminen.
- **Analysis**: Adjusted for Gender.

**Primary Endpoint (MEC):**
- **Overall**: 0 to 120 hours post-initiation of cisplatin chemotherapy.
- **Delayed Phase**: 25 to 120 hours post-initiation of chemotherapy.

**Overall Response:**
- **Standard Therapy**: 0 to 120 hours post-initiation of chemotherapy.
- **Oral Ondansetron**: 0 to 120 hours post-initiation of chemotherapy.
- **Fosaprepitant Regimen**: 0 to 120 hours post-initiation of chemotherapy.

**Comparison:**
- **Oral Ondansetron vs. Standard Therapy**: 0 to 120 hours post-initiation of chemotherapy.
- **Fosaprepitant Regimen vs. Standard Therapy**: 0 to 120 hours post-initiation of chemotherapy.

**Analysis:**
- **Analysis**: Miettinen and Nurminen.
- **Analysis**: Adjusted for Gender.

**MEC Response:**
- **MEC on Day 1 and the second dose was administered 8 hours after first ondansetron dose.**
- **Analysis**: Miettinen and Nurminen.
- **Analysis**: Adjusted for Gender.

**Confidence Interval:**
- **95% CI**: 95% confidence interval.

**Patient Demographics:**
- **Characteristics**:
  - **Sex**: M/F
  - **Age**: 18 to 70 years
  - **Body Weight**: 50 to 100 kg

**MEC on Day 1 and the second dose was administered 8 hours after first ondansetron dose.**

**Analysis:**
- **Analysis**: Miettinen and Nurminen.
- **Analysis**: Adjusted for Gender.

**Delayed Phase:**
- **Delayed Phase**: 25 to 120 hours post-initiation of chemotherapy.

**Comparison:**
- **Oral Ondansetron vs. Standard Therapy**: 25 to 120 hours post-initiation of chemotherapy.
- **Fosaprepitant Regimen vs. Standard Therapy**: 25 to 120 hours post-initiation of chemotherapy.

**Analysis:**
- **Analysis**: Miettinen and Nurminen.
- **Analysis**: Adjusted for Gender.

**Monitoring:**
- **Monitoring**: Blood tests, vital signs, and physical examination.

**Adverse Events:**
- **Adverse Events**: Vomiting, diarrhea, constipation.

**Interactions:**
- **Interactions**: CYP3A4 inhibitors, CYP3A4 inducers.

**Contraindications:**
- **Contraindications**: Hypersensitivity to fosaprepitant or any of its components.

**Warnings and Precautions:**
- **Warnings and Precautions**: Infusion site reactions (ISR) at or near the infusion site have happened with fosaprepitant for injection.
### Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
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<tr>
<td>Fosaprepitant Dimeglumine</td>
<td>(UNII: D35FM8T64X)</td>
<td>150 mg in 5 mL</td>
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<tr>
<td>Aprepitant</td>
<td>(UNII:1NF15YR6UY)</td>
<td>Fosaprepitant</td>
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### Inactive Ingredients

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<th>Strength</th>
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<tr>
<td>Edetate Sodium</td>
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<tr>
<td>Anhydrous Lactose</td>
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<td>Polysorbate 80</td>
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<tr>
<td>Sodium Hydroxide</td>
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<td>Hydrochloric Acid</td>
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### Packaging

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### Marketing Information

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<th>Marketing End Date</th>
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<td>ANDA209965</td>
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</table>

### Labeler - Dr. Reddy's Laboratories Inc.

- **Establishment Name**: MSL LABORATORIES PRIVATE LIMITED
- **Address**: 650786952
- **ID/FEI**: analysis(43598-948) , manufacture(43598-948)
- **Business Operations**: analysis(43598-948) , manufacture(43598-948)

*Revised: 3/2020*