On behalf of Heron Therapeutics, Inc. (Heron), I respectfully request the NCCN Antiemesis Guideline Panel to consider the enclosed data and information for aprepitant injectable emulsion in combination with other antiemetic agents in adults for prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV).

**Specific Changes:** The following changes are requested for the prevention of both acute and delayed CINV with both moderately emetogenic cancer chemotherapy (MEC) and highly emetogenic cancer chemotherapy (HEC):

- **HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY – ACUTE AND DELAYED EMESIS PREVENTION (page AE-5):**
  - Add aprepitant injectable emulsion as the preferred intravenous Neurokinin 1 (NK1) receptor antagonist (RA) in combination with a 5-HT3 receptor antagonist and dexamethasone (+/- olanzapine) with a category 1 recommendation
  - Dose: 130mg on Day 1

- **MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY – ACUTE AND DELAYED EMESIS PREVENTION (page AE-6):**
  - Add aprepitant injectable emulsion as the preferred intravenous NK1 RA in combination with a 5-HT3 receptor antagonist and dexamethasone with a category 1 recommendation
  - Dose: 130mg on Day 1 based on the bioequivalence study (2, 3, 4)

- Multi-day chemotherapy regimens likely to be moderately or highly emetogenic and associated with significant risk for delayed nausea and emesis (page AE-A) – Add aprepitant injectable emulsion as an option

- Management of breakthrough emesis +/- olanzapine (page AE-C) – Add aprepitant injectable emulsion as an option

**FDA Clearance:** On November 9, 2017, the FDA-approved aprepitant injectable emulsion in combination with other antiemetic agents in adults for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin, and nausea and vomiting associated with initial and repeat courses of MEC. Please refer to the enclosed full prescribing information for the FDA-approved indication, including safety information (1).

**Rationale:** Aprepitant injectable emulsion, an NK1 RA, demonstrated bioequivalence to fosaprepitant IV supporting its efficacy for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin, and nausea and vomiting associated with initial and repeat courses of MEC. In addition, aprepitant injectable emulsion demonstrated significantly fewer adverse events, including fewer infusion-site adverse events (ISAEs) and less frequent hypersensitivity systemic reactions (HSRs), compared to fosaprepitant. Finally, aprepitant injectable emulsion is the only IV formulation polysorbate 80 (PS80)-free FDA-approved for use in both the acute and delayed settings against both HEC and MEC.

**Supporting Literature:** Ottoboni et al. reported results of a Phase 1, open-label, randomized, 2-way crossover bioequivalence study comparing the pharmacokinetics and safety of aprepitant injectable emulsion and fosaprepitant. In this study, 97 healthy subjects who completed the trial received either a single dose of aprepitant injectable emulsion (130 mg) or fosaprepitant (150 mg). Plasma aprepitant concentrations were nearly identical 15 minutes through 72 hours post-infusion. Furthermore, mean AUC0-∞ (h*ng/mL), AUC0-24h, and C12h (ng/mL) for aprepitant injectable emulsion and fosaprepitant were within bioequivalence bounds (80%-125%), consistent for aprepitant exposure (90% CI). (2, 3, 4)

Fosaprepitant’s current formulation, which contains the surfactant PS80, is associated with ISAEs and HSRs, including pain, erythema, swelling, induration, and phlebitis or thrombophlebitis (5 - 13). Furthermore, studies are consistent with under-reporting of ISAEs and HSRs with fosaprepitant (5, 6, 9, 10, 11, 14). Recently, fosaprepitant’s FDA-approved label was revised to include a warning for anaphylactic shock and symptoms of hypotension and syncope (14). Unlike fosaprepitant, aprepitant injectable emulsion does not contain PS80. Ottoboni et al. evaluated the safety and tolerability of aprepitant injectable emulsion versus fosaprepitant (2, 3, 4). According to results, within the first 30 minutes of infusion, no subjects taking aprepitant injectable emulsion experienced ≥ 1 treatment emergent adverse event (TEAE), including HSRs, compared to 17% in subjects taking fosaprepitant. Within 1 hour of infusion, at least one TEAE occurred in 1% versus 20% of subjects receiving aprepitant injectable emulsion and fosaprepitant, respectively. During the entire study, fewer subjects experienced ≥ 1 treatment-related TEAE with aprepitant injectable emulsion compared to fosaprepitant (15% and 28%, respectively). TEAEs of pain in extremity were considered related to fosaprepitant. Furthermore, 3 subjects receiving fosaprepitant experienced dyspnea, 2 of whom had to discontinue the trial. Only one subject receiving aprepitant injectable emulsion experienced dyspnea, which was not felt to be related to study drug since it occurred on
day 5 following the infusion and was associated with an upper respiratory infection. Estimated event rate per subject-day for aprepitant injectable emulsion was approximately half the rate for fosaprepitant (negative binomial analysis, 0.03 versus 0.06 TEAEs per subject-day for aprepitant injectable emulsion vs. fosaprepitant, respectively, p=0.0274). Refer to table below for TEAEs in patients receiving aprepitant injectable emulsion or fosaprepitant. (2, 3, 4)

**Table 1. TEAEs in Patients Receiving Aprepitant or Fosaprepitant (≥3% of Patients Overall, Safety Population)**

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>Aprepitant injectable emulsion 130 mg, N = 99</th>
<th>Fosaprepitant IV 150 mg, N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache, n (%)</td>
<td>5 (5)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Infusion-site pain, n (%)</td>
<td>1 (1)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>1 (1)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Dizziness, n (%)</td>
<td>1 (1)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Dyspnea*, n (%)</td>
<td>1 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Pain in extremity, n (%)</td>
<td>0</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Somnolence, n (%)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*2 subjects receiving fosaprepitant discontinued the study due to moderate dyspnea.*

Based upon the current label there is a different aprepitant injectable emulsion dosing regimen for HEC and MEC. The HEC dosing refers to the fosaprepitant dose (150 mg IV on day 1) that was established in 2010. The fosaprepitant MEC dose had previously been 115 mg IV day 1 followed by days 2 and 3 oral aprepitant; however, this dosing schedule was changed in 2016 following completion of a MEC study which established 150 mg IV day 1 as an effective dose. The 3 year data exclusivity on this MEC data does not expire until 2019, at which time the MEC dosing for aprepitant injectable emulsion will be updated. Since the aprepitant injectable emulsion 130 mg dose was shown to be bioequivalent to fosaprepitant 150 mg as described above, we are requesting that the aprepitant injectable emulsion day 1 IV dose of 130 mg be recommended for both HEC and MEC.

In summary, aprepitant injectable emulsion demonstrates bioequivalence to fosaprepitant with lower incidence of ISAEs and HSRs compared to fosaprepitant, thus providing a safer alternative for the prevention of CINV. Further, aprepitant injectable emulsion is the only IV formulation PS80-free FDA-approved NK1 RA for use in both the acute and delayed settings against both HEC and MEC. Therefore, we respectfully request inclusion of aprepitant injectable emulsion as the preferred intravenous NK1 RA in combination with a 5-HT3 receptor antagonist and dexamethasone with a category 1 recommendation for the prevention of CINV associated with initial and repeat courses of HEC (+/- olanzapine) and MEC as described above. Thank you for your time and consideration.

Robert B. Geller, MD
Vice President, Medical Affairs, Heron Therapeutics

References (underlined enclosed)

14. [https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/022023Orig1s016tir.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/022023Orig1s016tir.pdf)