CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210493Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
<table>
<thead>
<tr>
<th><strong>Application Type</strong></th>
<th>NDA</th>
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<td><strong>Application Number</strong></td>
<td>210493</td>
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<tr>
<td><strong>PDUFA Goal Date</strong></td>
<td>April 28, 2018</td>
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<td><strong>OSE RCM #</strong></td>
<td>2017-1128</td>
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<tr>
<td><strong>Reviewer Name</strong></td>
<td>Erin M. South, PharmD, DRISK</td>
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<td><strong>Team Leader</strong></td>
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<td><strong>Review Completion Date</strong></td>
<td>January 2, 2018</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Evaluation of Need for a REMS</td>
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<tr>
<td><strong>Established Name</strong></td>
<td>fosnetupitant / palonosetron</td>
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<tr>
<td><strong>Trade Name</strong></td>
<td>Akynzeo for injection</td>
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<tr>
<td><strong>Name of Applicant</strong></td>
<td>Helsinn Healthcare, SA</td>
</tr>
<tr>
<td><strong>Therapeutic Class</strong></td>
<td>Anti-Emetics/Serotonergics</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>235 mg fosnetupitant/0.25 mg palonosetron lyophilized powder in single-dose vial for reconstitution</td>
</tr>
<tr>
<td><strong>Dosing Regimen</strong></td>
<td>One vial of Akynzeo; infuse over 30 minutes starting 30 minutes before start of chemotherapy</td>
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Akynzeo for injection is necessary to ensure the benefits of this product outweigh its risks. On April 20, 2017, Helsinn Healthcare, SA (hereinafter, referred to as Helsinn or the Applicant) submitted a New Drug Application (NDA 210493, Akynzeo) for a fixed-dose combination (FDC) product containing 235 mg fosnetupitant/0.25 mg palonosetron lyophilized powder in a single-dose vial for reconstitution. The proposed indication is for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC). The most important risks associated with the use of the proposed formulation of Akynzeo for injection include hypersensitivity reactions and serotonin syndrome, both of which are included in the Prescribing Information for Akynzeo oral capsules (NDA 205718, approved October 10, 2014). The Applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Gastrointestinal and Inborn Errors Products (DGIEP) agree that a REMS is not needed to ensure the benefits of Akynzeo for injection outweigh its risks. This product has proven to prevent acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, not including anthracycline plus cyclophosphamide chemotherapy. Based on the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required. Furthermore, healthcare providers who treat patients with cancer who experience nausea and vomiting associated with HEC treatment are informed of these risks as they are included in the labeling for the currently marketed Akynzeo oral capsules.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure the benefits outweigh the risks for the new molecular entity (NME) Akynzeo, proposed as a fixed-dose combination (FDC) product containing fosnetupitant and palonosetron for intravenous (IV) injection. On April 20, 2017, Helsinn Healthcare, SA (hereinafter, referred to as Helsinn or the Applicant) submitted a New Drug Application (NDA 210493, Akynzeo) for a fixed-dose combination product containing 235 mg fosnetupitant/0.25 mg palonosetron lyophilized powder in single-dose vial for reconstitution. The proposed indication is for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC). This application is under review in the Division of Gastrointestinal and Inborn Errors Products (DGIEP). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information
Akynzeo for injection is proposed as a FDC product containing fosnetupitant and palonosetron. Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK1) receptors. Netupitant was developed into the prodrug fosnetupitant and is currently considered an NME. Palonosetron is a serotonin (5-HT3) receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Akynzeo oral capsules (FDC netupitant and palonosetron HCl) was approved in October 2014 under NDA 205718 for the prevention of acute and delayed chemotherapy-induced nausea and vomiting and is currently marketed in the U.S. Palonosetron is additionally marketed individually as Aloxı, which is indicated for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately-emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC) and for prevention of delayed nausea in MEC. In addition to being marketed in the U.S., oral Akynzeo is also currently marketed in Europe.

Akynzeo would be used mainly in an outpatient infusion setting. The proposed dosing regimen is for administration of one vial as a 30-minute intravenous infusion starting 30 minutes prior to the start of chemotherapy. The proposed dosing recommendations also state that dexamethasone 12 mg should be administered 30 minutes prior to chemotherapy, followed by dexamethasone 8 mg once a day on Days 2 to 4; and the treatment duration is weeks to months.a

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for NDA 210493 relevant to this review:

- 10/10/2014: Approval of NDA 205718 for Akynzeo (netupitant and palonosetron) oral capsules, a FDC for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC.

- 4/20/2017: NDA 210493 submission received for a FDC product containing 235 mg fosnetupitant/0.25 mg palonosetron lyophilized powder in a single-dose vial for reconstitution. The proposed indication is for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

- 10/3/2017: The Mid-Cycle Communication Meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that, based on the currently available data, there were no safety issues that require a REMS for Akynzeo for injection.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION1
Chemotherapy-induced nausea and vomiting (CINV), particularly nausea, is cited by cancer patients as having the greatest impact on their quality of life. Risk factors for CINV include young age, female sex, platinum- or anthracycline-based chemotherapy, non-drinker status, emesis in the earlier cycles of chemotherapy, and a previous history of motion or morning sickness. Patients who are undergoing

a FDAAA factor (D): The expected or actual duration of treatment with the drug
chemotherapy can experience nausea and vomiting in the acute phase (0-24 hours after chemotherapy initiation), the delayed phase (>24-120 hours after chemotherapy administration), or the overall phase (0-120 hours after chemotherapy administration).

The emetogenicity of the chemotherapy also has an impact on CINV. In general, the emetic risk associated with HEC is ≥ 90%. For MEC, the emetic risk ranges from 30-90 percent. The medications included in HEC include, but are not limited to, cisplatin, carmustine, cyclophosphamide, dacarbazine, mechlorethamine, and streptozocin. \(^b\) In 2011, the American Society of Clinical Oncology (ASCO) reclassified anthracycline-cyclophosphamide (AC) chemotherapy combinations from MEC to HEC, even though the likelihood of emesis on these medications without antiemetic prophylaxis was 85% while the rest of the medications in HEC were 90% or greater. \(^c\)

#### 3.2 Description of Current Treatment Options

With respect to CINV, there are two main classes of medications that are used: neurokinin 1 (NK1) receptor antagonists and serotonin (5-HT3) receptor antagonists. 5-HT3 antagonists are thought to work in the acute phase, whereas NK1 inhibitors are thought to work in both the acute phase and the delayed phase. The only exception to this is IV palonosetron, which has an indication for delayed phase MEC.

The 2017 ASCO guidelines recommend that adult patients who are treated with cisplatin and other high-emetic-risk single agents should be offered the four-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine. Dexamethasone and olanzapine should be continued on days 2 to 4. \(^1\) Adult patients who are treated with an anthracycline combined with cyclophosphamide should be offered a four-drug combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine. Olanzapine should be continued on days 2 to 4. \(^1\)

<table>
<thead>
<tr>
<th>5HT3</th>
<th>Dosage Form</th>
<th>HEC vs MEC, Acute vs Delayed Phase</th>
<th>Year Approved</th>
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</thead>
<tbody>
<tr>
<td>Zofran (Ondansetron)</td>
<td>Oral and IV</td>
<td>Oral – HEC and initial and repeat courses of MEC IV - Nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy</td>
<td>IV-1991, Oral -1992</td>
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<tr>
<td>Anzemet (Dolasetron)</td>
<td>Oral and IV</td>
<td>Oral - Initial and repeat MEC in patients ≥2 years old IV – indications are for postoperative nausea and vomiting</td>
<td>Oral and IV - 1997</td>
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</table>


\(^c\) [www.asco.org/guidelines/antiemetics](www.asco.org/guidelines/antiemetics)
<table>
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<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>Indication (HEC vs MEC, Acute vs Delayed Phase)</th>
<th>Year Approved</th>
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<tr>
<td>Kytril/ Sustol</td>
<td>Oral, IV, extended Injection (Systol)</td>
<td>Kytril (discontinued) - Initial and repeat courses emetogenic cancer chemotherapy, including high dose cisplatin. Sustol - prevention of acute and delayed nausea and vomiting with initial and repeat MEC and AC</td>
<td>Kytril - 1993, Sustol - 2016</td>
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<tr>
<td>NK1</td>
<td>Dosage Form</td>
<td>Indication (HEC vs MEC, Acute vs Delayed Phase)</td>
<td>Year Approved</td>
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<tr>
<td>Emend (aprepitant/fosaprepitant)</td>
<td>Oral and IV</td>
<td>Oral – Initial and repeat courses for acute and delayed HEC. Initial and repeat courses of MEC IV – delayed nausea and vomiting associated with initial and repeat MEC</td>
<td>HEC - 2003, MEC - 2005</td>
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<tr>
<td>Varubi (rolapitant)</td>
<td>Oral</td>
<td>Prevention of delayed nausea and vomiting with initial and repeat courses including but not limited to HEC</td>
<td>2015</td>
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<tr>
<td>5HT3 and NK1</td>
<td>Dosage Form</td>
<td>HEC vs MEC, Acute vs Delayed Phase)</td>
<td>Year Approved</td>
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<tr>
<td>Akynzeo* capsules</td>
<td>Oral</td>
<td>“including but not limited to HEC” acute and delayed phases</td>
<td>2014</td>
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</table>


4 Benefit Assessment

Akynzeo for injection (fosnetupitant and palonosetron FDC) is proposed for an indication in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC). The oral dosage form of Akynzeo (netupitant and palonosetron) is approved with an HEC indication. According to the clinical reviewer, evidence of the effectiveness of Akynzeo for injection to support this application includes the following:

1. Studies that supported the approval of Akynzeo capsules: Akynzeo capsules are indicated for HEC including anthracycline/cyclophosphamide (AC) based chemotherapy in both the acute and delayed phases. The effect of palonosetron was demonstrated in the acute phase, and the effect of netupitant was demonstrated in both the acute and delayed phases.
2. Studies that supported the approval of Aloxib (palonosetron) IV: Aloxib (palonosetron) IV is indicated for HEC in the acute phase; and for moderately emetogenic chemotherapy (MEC) in both the acute and delayed phases. It should be noted that the studies supporting this indication were based on a former classification of HEC and MEC where HEC did not include AC, and MEC included AC.
3. Studies submitted in the current NDA: These are described below.

Study PALO 15-17: Non-inferiority Study (palonosetron 30-minute infusion vs. 30-second infusion)
Study PALO 15-17 was a Phase 3, single-dose, multicenter, randomized, double-blind, parallel group study to assess the efficacy and safety of palonosetron 0.25 mg administered as a 30-minute IV infusion compared to palonosetron 0.25 mg administered as a 30-second IV bolus for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving HEC. A total of 441 subjects were randomized equally into the two treatment groups. Subjects were adults ≥ 18 years of age with a confirmed solid tumor malignancy, naïve to cytotoxic chemotherapy, and scheduled to receive their first course of HEC alone or in combination with other chemotherapeutic agents on Day 1. The primary endpoint was a complete response (CR, defined as no emetic episode and no use of rescue medication) in the 24 hours (acute phase) after the start of the scheduled chemotherapy.

Additional data was derived from Studies PNET 12-23 and NEPA 15-18, which are described below.

Study PNET 12-23: Pivotal Relative Bioavailability Study (IV fosnetupitant vs. oral netupitant)
A single-center, Phase 1 relative bioavailability study in 158 healthy subjects, which included a comparison of the area under the curve (AUC) of netupitant between 260 mg of IV fosnetupitant (a prodrug of netupitant) and 300 mg of oral netupitant (the dose of netupitant in the approved Akynzeo capsules).

Study NEPA 15-18: Active Control Study (Akynzeo for infusion vs. Akynzeo oral capsules)
Study NEPA 15-18 was a Phase 3, multicenter, randomized, double-blind, active control study to evaluate the safety and efficacy of IV pro-netupitant 260 mg/palonosetron 0.25 mg FDC for the prevention of chemotherapy-induced nausea and vomiting in 405 subjects. This study was conducted primarily to analyze the safety and tolerability of pro-netupitant 260 mg/palonosetron 0.25 mg FDC infused over 30 min., with oral dexamethasone, in initial and repeated, up to a total of four, cycles of HEC. Since efficacy assessment was a secondary study objective, only descriptive statistics were planned and performed. The secondary endpoints included the proportion of subjects with a CR with no rescue medication during the acute phase, delayed phase (>24 to 120 hours after the start of chemotherapy), and overall phase (0 to 120 hours after the start of chemotherapy).

The efficacy data in this study was analyzed using descriptive statistics. According to the clinical reviewer, the trial was neither designed nor powered to be a non-inferiority study. Additionally, protocol deviations impacted the efficacy results. Overall, 27 (6.7%) patients in the FAS had protocol deviations with a major impact on efficacy at Cycle 1: 13 (6.4%) patients in the IV group and 14 (7.0%) patients in the oral group. The most common protocol deviation referred to “use of medications with potential antiemetic effects or use of CYP3A4 strong or moderate inhibitors, use of CYP3A4 inducers or substrates during Cycle 1 in the interval 0-120 hours after start of reference HEC.” The clinical reviewer concluded that the data from this study cannot be used to make a statistically meaningful comparison of efficacy between oral and IV formulations. Therefore, the reviewer concluded, data from this trial was not critical to the efficacy evaluation for NDA 210493.

**Analysis Populations**
The Full Analysis Set (FAS) includes all patients who have been randomized to treatment and received HEC regimen and active study drug (including partial infusion). The Per-Protocol (PP) population included all patients from the FAS, who had completed the 0-24 hour study period and with no major protocol violations.

Clinical Efficacy Results

In the non-inferiority study, PALO 15-17, 186 (82.7%) patients in the infusion group reported a complete response (CR) in the acute phase, as did 186 (86.5%) patients in the bolus group. The difference in proportion between the 30-min. infusion and 30-sec. bolus treatment groups was -3.8% (99% CI: -12.2%, 4.7%). The clinical reviewer concluded that, since the lower limit of the two-sided 99% CI for the difference in proportions was greater (i.e., closer to zero) than the pre-defined non-inferiority margin of -15%, non-inferiority of palonosetron 30-min. infusion compared to 30-sec. bolus was demonstrated.

In the relative bioavailability study, PNET 12-23, the IV/oral ratio was 0.94 (90% CI: 0.88 – 1.01) for AUC\text{12h} and 0.88 (90% CI: 0.82 – 0.94) for AUC\text{∞}. According to the clinical pharmacology reviewer, the systemic exposures to netupitant met bioequivalence criteria. The clinical pharmacology reviewer added, “Although the final proposed product is a combination of fosnetupitant and palonosetron, while fosnetupitant as a single agent was used in the pivotal bioequivalence study, the presence of palonosetron does not affect the pharmacokinetics of fosnetupitant.”

To summarize, the clinical reviewer determined that the effect of IV palonosetron infused over 30 minutes was demonstrated in the acute phase in the population of HEC not including anthracycline/cyclophosphamide-based chemotherapy (AC); and the effect of IV fosnetupitant was demonstrated in the acute and delayed phases in the same population. Based on the results of the clinical trials, the clinical reviewer concluded that palonosetron prevents nausea and vomiting during the acute phase and fosnetupitant prevents nausea and vomiting during both the acute and delayed phases after cancer chemotherapy. Therefore, the clinical reviewer is recommending approval of Akynzeo for injection in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, not including anthracycline plus cyclophosphamide chemotherapy.

5 Risk Assessment & Safe-Use Conditions

NEPA 15-18 was the primary safety study because it involved cancer patients receiving HEC and both components of the proposed Akynzeo formulation for IV injection. Data from PNET 12-23 and PALO 15-17 also supported the safety review for this NDA.

The most important treatment-emergent adverse events (TEAEs), hypersensitivity reactions and serotonin syndrome, are addressed in the label for the approved Akynzeo oral formulation. Both the oral and IV formulations of Akynzeo are expected to share the same Prescribing Information.

According to the clinical review of safety, TEAEs were evenly balanced between the two treatment arms. The currently approved Prescribing Information for Akynzeo oral capsules includes the following most

Reference ID: 4202372
common adverse events (incidence ≥3% and greater than palonosetron): headache, asthenia, dyspepsia, fatigue, constipation, and erythema. According to the clinical reviewer, when the safety data were analyzed using shift tables, the numbers of subjects with normal creatinine levels that became elevated by the end of the study was similar between the two treatment arms. Nausea was considered part of the underlying disease (i.e., CINV) rather than a treatment-emergent adverse event.

The clinical reviewer concluded that no new safety signals were identified in Studies NEPA 15-18, PNET 12-23, and PALO 15-18; and, from a safety perspective, the proposed Akynzeo formulation for injection poses no additional risks to cancer patients compared to Akynzeo oral capsules. At the time of this review, labeling negotiations are ongoing.

6 Expected Postmarket Use

Akynzeo for injection is expected to be prescribed by oncology healthcare providers and administered primarily by nursing staff in an outpatient infusion setting. The recommended dosage is 1 vial of Akynzeo lyophilized powder for injection, containing 235 mg fosnetupitant/0.25 mg palonosetron, to be reconstituted in 50 mL of 5% dextrose for injection, USP or 0.9% sodium chloride for injection, USP, infused over 30 minutes, starting 30 minutes before chemotherapy.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Akynzeo for injection beyond routine pharmacovigilance and labeling. The clinical reviewer is recommending the following two Post-Marketing Requirements (PMRs):

- An 8-week toxicology study with fertility evaluation in neonatal rats treated with fosnetupitant (pro-netupitant) alone; and
- An open-label, pharmacokinetic and safety study of intravenous (IV) pro-netupitant / palonosetron combination in pediatric cancer patients ages 0-17 years for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

8 Discussion of Need for a REMS

The benefits of treatment with Akynzeo for injection were demonstrated by meeting the primary endpoints of the clinical trials. Akynzeo for injection was found to be efficacious. From a safety perspective, the proposed Akynzeo formulation for injection poses no additional risks to patients.
compared to Akynzeo oral capsules, which were approved in October 2014 without a REMS or boxed warning.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable. Therefore, it is the opinion of this reviewer that a REMS is not necessary to ensure the benefits of fosnetupitant/palonosetron FDC for injection outweigh its risks. At the time of this review, labeling negotiation is ongoing, with both the oral and IV formulations expected to share Prescribing Information. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should DGIEP have any concerns or questions, or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES


This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIN M SOUTH
01/02/2018

JAMIE C WILKINS PARKER
01/02/2018