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RESEARCH**

APPLICATION NUMBER:

205718Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 205,718
Product Name: Akynzeo

PMR/PMC Description: An 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with netupitant alone.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>05/30/2015</u>
	Study/Trial Completion:	<u>12/30/2015</u>
	Final Report Submission:	<u>03/30/2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A juvenile animal toxicity study with netupitant alone is needed to assure safety in a postmarketing pediatric trial of netupitant + palonosetron fixed dose combination to evaluate safety and efficacy. Dosing in the juvenile animal study should begin at a developmental stage comparable to the human neonatal stage. Based on results of the combination toxicity studies of netupitant + palonosetron in adult rats and dogs, and the toxicity profile of palonosetron alone in neonatal rats, juvenile animal studies with the drug combination are not considered necessary to support the pediatric study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

An oral toxicity study with netupitant alone of at least 8 weeks duration in neonatal rats is needed to support the enrollment of patients age 0 to < 12 years in the proposed pediatric clinical efficacy and safety study in patients age 0 to < 17 years. The neonatal rat study should include evaluation of developmental parameters, neurobehavioral effects, and fertility.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An oral toxicity study with netupitant alone of at least 8 weeks duration in neonatal rats is needed. This study should include evaluation of developmental parameters, neurobehavioral effects, and fertility.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 205718
Product Name: Akynzeo (netupitant + palonosetron fixed dose combination) Capsule

PMR/PMC Description: A PK/PD dose finding study of netupitant to characterize netupitant PK/PD relationship for complete response in the delayed phase following oral administration of single dose of netupitant given concomitantly (in separate formulations) with oral single administration of palonosetron in pediatric cancer patients ages 0 to 17 years undergoing treatment with emetogenic chemotherapy including highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>11/01/2015</u>
	Study/Trial Completion:	<u>04/30/2018</u>
	Final Report Submission:	<u>09/30/2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The sponsor will need to develop an age appropriate formulation of netupitant alone to administer with IV Aloxi, given orally, for use in pediatric patients. Only after the age appropriate formulation of netupitant alone is developed and found suitable for use can the PK/PD study commence. The timeline for final protocol submission must allow sufficient time for the sponsor to develop the netupitant formulation.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Study #1 is planned to be a PK/PD study in pediatric cancer patients to characterize netupitant PK/PD relationship when administered concomitantly with the approved dose of palonosetron. The PD parameter to be measured is complete response. Doses for both drugs are planned to be based on body weight from 0 to 17 years of age in patients undergoing treatment with emetogenic chemotherapy.

Based and contingent upon formulation development outcomes, an age appropriate oral formulation of netupitant-alone will be used and it will be administered concomitantly with I.V. Aloxi given orally. The acceptability of the oral use of I.V. Aloxi in pediatric cancer patients was already agreed with FDA for the Written Request program of Aloxi NDA 21372.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug

- There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 205718
Product Name: Akynzeo (netupitant + palonosetron FDC) capsules

PMR/PMC Description: An adequate, well-controlled, double-blind, randomized, study to evaluate the safety and efficacy of a dose of the netupitant-palonosetron fixed dose combination compared to standard therapy in pediatric cancer patients ages 0 to 17 years undergoing treatment with emetogenic chemotherapy including highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/30/2019</u>
	Study/Trial Completion:	<u>12/31/2021</u>
	Final Report Submission:	<u>04/30/2022</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

PREA required safety and efficacy trial

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the trial is to obtain safety and efficacy data in order to inform labeling for pediatric use.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An adequate, well-controlled, double-blind, randomized, study to evaluate the safety and efficacy of a dose of the netupitant-palonosetron FDC compared to standard therapy in pediatric cancer patients from 0 to 17 years of age undergoing treatment with emetogenic chemotherapy. Study #2 is planned to be an add-on superiority trial of the FDC versus vs. palonosetron, or a non-inferiority study of the FDC versus aprepitant used with palonosetron. The final age appropriate pediatric oral formulation of the netupitant + palonosetron FDC is planned to be used in this trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
PREA Efficacy and Safety Study
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 205718
Product Name: Akynzeo® (netupitant-palonosetron hydrochloride) Capsule

PMR/PMC Description: In-vivo drug interaction study to evaluate the duration of inhibitory effects of AKYNZEO on CYP3A4 enzyme activity beyond 4 days after AKYNZEO administration

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/31/2015</u>
	Study/Trial Completion:	<u>01/31/2016</u>
	Final Report Submission:	<u>06/30/2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The sponsor conducted two drug interaction studies to address the inhibition of CYP3A4 enzyme activity by netupitant. Nevertheless, it was found that the information was insufficient to fully characterize the duration of CYP3A4 enzyme inhibition. The estimation based on in-vitro assays suggest that drug interaction is possible even on Day 6 after single dose administration of netupitant, a component of Akynzeo. Therefore, an additional study is being committed to confirm the estimation as well as the worst case scenario. In the meantime, the labeling will state the observed drug interaction via inhibition of CYP3A4 as well as the duration of such inhibition at least for 4 days based on study results.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Co-administration of a single dose of netupitant increased the exposure to dexamethasone, a substrate of CYP3A4 by 1.7-fold on Day 1 and up to 2.4-fold on Day 2 and Day 4. The potential inhibitory effect of netupitant on CYP3A4 was not studied beyond Day 4. Given AKYNZEO will be used in patients who require multiple medications for underlying disease treatment as well as supportive care, a study is necessary to provide adequate information for use of AKYNZEO with concomitant medications that are CYP3A4 substrates.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study design will include healthy subjects who will receive a regimen of dexamethasone alone administered for up to 6 days and beyond (Treatment A) and the same regimen of dexamethasone plus AKYNZEO on day 1 only (Treatment B), according to a two-period, two-sequence, randomized crossover design.

The PK profile of dexamethasone will be fully described on different days throughout the study duration, with/without the single AKYNZEO administration. The PK profile of netupitant and its metabolites M1, M2 and M3 will also be followed in parallel. Data analysis will primarily compare the AUC_t of dexamethasone with/ without netupitant co-administration, in order to determine the duration of CYP3A4 inhibition. Additional analysis will consider the ratios of trough dexamethasone concentrations over time with / without netupitant co-administration.

Required

- Observational pharmacoepidemiologic study
- Registry studies

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
In vivo drug interaction study in healthy subjects
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Assessment of potential interaction of netupitant with P-gp as substrate will be based on the bi-directional transport methodology and utilize polarized monolayer cells as the functional assay. Bi-directional transport will be performed in human colon adenocarcinoma (Caco-2) cells seeded on polycarbonate microporous membrane filters.

Apparent Permeability Coefficient (Papp) in $\text{cm} \cdot 10^{-6} / \text{sec}$ and efflux ratio value will be determined.

Standard compound included in each permeability assay are: Digoxin, as P-gp substrate, Cyclosporine A and Verapamil, as P-gp inhibitors.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
In vitro study
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

MARY H CHUNG
09/10/2014

RUYI HE
09/10/2014



M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 4, 2014

To: Donna Griebel, M.D., Director
Division of Gastroenterology and Inborn Error Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Statement on Section 9.0 of drug label
Akynzeo (Netupitant and Palonosetron HCl Fixed-Dose
Combination Capsule)
NDA 205,718 (IND 73,493)
Indication: Prevention of acute and delayed nausea and
vomiting associated with cancer chemotherapy
Sponsor: Helsinn Healthcare, SA
PDUFA Goal Date: September 26, 2014

Background

This memorandum responds to a request by the Division of Gastroenterology and Inborn Error Products to evaluate a proposal from Helsinn Healthcare on August 1, 2014 to exclude Section 9.0 (Drug Abuse and Dependence) from the drug label for Akynzeo (Netupitant and Palonosetron HCl Fixed-Dose Combination Capsule).

The Sponsor states that their proposal is supported by a statement in the FDA *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (2013) that, “The Drug Abuse and Dependence section should be omitted for a drug that is not a controlled substance and has no potential for abuse or dependence.”

CSS previously concluded in our May 30, 2014, consult that Akynzeo has no potential for abuse or dependence.

Conclusion and Recommendation

CSS accepts the Sponsor's proposal to eliminate Section 9.0 from the drug label for Akynzeo, based on the *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (2013).

This recommendation replaces our previous recommendation in our May 30, 2014, consult that the drug label should include brief information in Section 9.0 about abuse-related study data showing that netupitant + palonosetron has no potential for abuse or dependence.

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/s/

KATHERINE R BONSON
08/04/2014

SILVIA N CALDERON
08/04/2014

MICHAEL KLEIN
08/04/2014

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 205718

Application Type: New NDA

Name of Drug/Dosage Form: Akynzeo (netupitant/palonosetron HCl) fixed-dose combination capsule

Applicant: Helsinn Healthcare, Inc.

Receipt Date: September 27, 2013

Goal Date: September 26, 2014

1. Regulatory History and Applicant's Main Proposals

On September 15, 2006, Helsinn Healthcare submitted IND 73493 for netupitant/ palonosetron fixed-dose combination capsules for treatment of chemotherapy induced nausea and vomiting. Helsinn's clinical development program was discussed at the end-of-phase 2 meeting held on July 20, 2009. A series of Special Protocol Assessment (SPA) requests were submitted by the sponsor and Type A SPA meetings were held January 22, 2010 and July 15, 2010. Per discussion from these meetings, four clinical studies (NETU-07-07, PALO-10-01, NETU-08-18, and NETU-10-29) were conducted to support the efficacy and safety of the fixed-dose combination capsule for the prevention of acute and delayed phases of CINV-HEC and CINV-MEC. On April 16, 2013, a pre-NDA meeting was held to discuss the results of the phase 3 trials, the content and format of the planned eCTD NDA submission, proposed labeling and the schedule to submit the pediatric study plan.

On September 27, 2013, Helsinn Healthcare submitted NDA 205718 for the following indications:

1. Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (CINV HEC).
2. Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV MEC).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

Selected Requirements of Prescribing Information

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 6, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- NO** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *Highlights must be one-half page or less unless a waiver has been granted in a previous submission.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

Selected Requirements of Prescribing Information

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product)**".

Selected Requirements of Prescribing Information

safely and effectively. See full prescribing information for (insert name of drug product).”
The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A

Selected Requirements of Prescribing Information

18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Selected Requirements of Prescribing Information

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- NO** 25. The TOC should be in a two-column format.
Comment: The Table of Content (TOC) should be in a two-column format.
- YES** 26. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment: The subsection headings are indented but bolded. The word “action” in subsection 12.1 must be capitalized.
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: The numbers 9 and 15 must be deleted from the TOC.
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Subsections "8.6 Hepatic Impairment" and "8.7 Renal Impairment" were additionally added under "Section 8 Use in Specific Population" according to 21 CFR 201.56(d)(2).

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment: Several references are not italicized

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

NO

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *The reference "See FDA-approved Patient Labeling" should indicate type of FDA-approved patient labeling (i.e., Patient Information).*

- NO** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *FDA-approved patient labeling must not be included as a subsection under section 17.*

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

MARY H CHUNG

08/04/2014

Review completed 11/26/2013



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 30, 2014

To: Donna Griebel, M.D., Director
Division of Gastroenterology and Inborn Error Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Evaluation of Abuse-Related Studies
Akynzeo (Netupitant and Palonosetron HCl Fixed-Dose
Combination Capsule) (300 mg netupitant + 0.5 mg
palonosetron in hard gelatin capsules for oral administration)
NDA 205,718 (IND 73,493)
Indication: Prevention of acute and delayed nausea and
vomiting associated with initial and repeat courses of cancer
chemotherapy, including highly emetogenic chemotherapy
(HEC)
Sponsor: Helsinn Healthcare, SA
PDUFA Goal Date: September 26, 2014

Materials reviewed: Abuse-related preclinical and clinical data in NDA
submission (eCTD 0000, 9/27/13)

Table of Contents

1	BACKGROUND	2
2	CONCLUSIONS	2
3	RECOMMENDATIONS.....	4
4	DISCUSSION	5

1. Background

This memorandum responds to a consult request by the Division of Gastroenterology and Inborn Error Products (DGIEP) to evaluate abuse-related preclinical and clinical data submitted by Helsinn Healthcare in NDA 205,718 for Akynzeo (Netupitant and Palonosetron HCl Fixed-Dose Combination Capsule). This product is a drug combination in a hard gelatin capsule that contains three 100 mg netupitant tablets and one palonosetron 0.50 mg soft gelatin capsule for oral administration. The drug product is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including highly emetogenic chemotherapy (HEC). The recommended dose is one capsule administered approximately one hour prior to the start of chemotherapy. Since chemotherapy typically consists of multiple exposures to anti-neoplastic agents over multiple cycles, Akynzeo will be used by patients on a chronic basis.

Netupitant is a new molecular entity that is a neurokinin (NK)-1 receptor antagonist. The first-in-class NK-1 antagonist, aprepitant (Emend), was approved in the U.S. in 2006 for the prevention of postoperative nausea and vomiting. The drug label for Emend does not contain Section 9.0 Drug Abuse and Dependence, suggesting there are no abuse-related data available for aprepitant. The NDA for another NK-1 antagonist, casopitant, was withdrawn in 2009 because of concerns regarding cardiovascular toxicity.

Palonosetron (Aloxi) is a 5HT₃ antagonist that was approved in the U.S. in 2003. Aloxi is marketed in two formulations (0.25 mg, i.v. and 0.5 mg, p.o.) for use in the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic chemotherapy. The drug label for Aloxi does not contain Section 9.0 Drug Abuse and Dependence, suggesting there are no abuse-related data available for palonosetron.

There are currently no netupitant + palonosetron drug combinations marketed in any country. However, in January 2014, a Marketing Authorisation Application submitted by Helsinn Healthcare was accepted for review by the European Medicines Agency (EMA) for a combination product containing netupitant + palonosetron. Neither netupitant or palonosetron is a scheduled substance under the Controlled Substances Act (CSA).

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 205,718 for the netupitant + palonosetron drug combination (Akynzeo) and concludes that this drug combination does not have abuse potential. Notably, many studies were conducted with netupitant alone, since it is a new molecular entity that has not been evaluated previously for abuse potential. The conclusion that netupitant + palonosetron does not have abuse potential is based on the results from the following:

- Receptor binding studies show that palonosetron is a high affinity 5HT₃ ligand and that netupitant is a high affinity ligand at NK-1 receptors. Netupitant also

induces 67% inhibition at the dopamine transporter and 75-100% inhibition at calcium channels, but these data were not converted to K_i values. The abuse-related binding profile for netupitant is incomplete because it did not test the affinity of netupitant for dopamine, glutamate, cannabinoid and 5HT₂ receptors. However, an evaluation of the behavioral signs in animal studies conducted with netupitant does not show any abuse-related signals, as described below.

- Four toxicology studies with netupitant (with or without palonosetron) were conducted in rats (for 13 and 26 weeks) and beagle dogs (for 13 weeks and 9 months), each with an 8-week recovery period. There were no abuse-related behaviors observed during the drug administration period and no withdrawal-like behaviors observed during the drug discontinuation period.
- In a pharmacokinetic/pharmacodynamic study in baboons with netupitant + palonosetron, there were no behavioral effects observed.
- In an Irwin study of general behavior with rats, there were no abuse-related behaviors observed following administration of netupitant alone.
- In a drug discrimination study with baboons, netupitant + palonosetron did not generalize to either a sedative benzodiazepine (lorazepam or diazepam) or to the stimulant/hallucinogen MDMA. These data suggest that netupitant + palonosetron does not produce activity similar to that of a GABA agonist or an inhibitor of the dopamine/serotonin transporter.
- In a self-administration study with baboons, netupitant + palonosetron did not produce levels of self-administration that were different from those produced by vehicle. These data suggest that netupitant + palonosetron does not produce rewarding effects.
- In physical dependence studies conducted in rats, beagle dogs and olive baboons, chronic administration of netupitant + palonosetron, or netupitant alone, did not produce withdrawal-like behaviors upon drug discontinuation. This suggests that netupitant (with or without palonosetron) does not produce physical dependence.
- In human pharmacokinetic studies, netupitant has a T_{max} of 4-5 hours and an elimination half-life of 30-100 hours. Palonosetron has a T_{max} of 3-6 hours and an elimination half-life of 40-50 hours.
- In humans, 3 major metabolites of netupitant (M1, M2 and M3) are produced, representing 11%, 47% and 16% of the parent drug, respectively. Since there are no abuse-related behavioral signals associated with chronic administration of netupitant alone (or with palonosetron) in humans, the data do not suggest that any of the active metabolites of netupitant have abuse potential. There are no major metabolites of palonosetron.

- Clinical studies conducted with netupitant + palonosetron in healthy individuals and in cancer patients do not show a pattern of adverse events (AEs) indicative of abuse potential. The most frequently reported central nervous system (CNS)-related AE was headache (2.4%).

The draft label submitted by the Sponsor does not include Section 9.0 (Drug Abuse and Dependence), based on their conclusion that netupitant + palonosetron does not have abuse potential. Although CSS agrees with this conclusion, based on the data described above, Section 9.0 should be added to the drug label and should accurately reflect the abuse-related study data submitted in the NDA for netupitant + palonosetron.

3. Recommendations

- CSS recommends the addition of Section 9.0 (Drug Abuse and Dependence) to the drug label for netupitant + palonosetron, with the following language:

Section 9.0 (Drug Abuse and Dependence)

9.1 Controlled Substance

Akynzeo (a drug product containing netupitant and palonosetron) is not scheduled under the Controlled Substances Act.

9.2 Abuse

The drug combination of netupitant and palonosetron does not produce any signs indicative of abuse potential in preclinical or clinical studies.

9.3 Dependence

In physical dependence studies conducted in rats, beagle dogs and olive baboons, chronic administration of netupitant and palonosetron did not produce withdrawal-like behaviors upon drug discontinuation. These data suggest that netupitant and palonosetron does not produce physical dependence.

- CSS and CDER should not recommend the netupitant + palonosetron drug combination for control under the CSA, because the results from abuse potential studies show that the drug combination lacks abuse potential.

4. Discussion

A. Chemistry of Netupitant

Netupitant is 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl]propanamide. It is a white to off-white crystalline powder that is freely soluble in toluene and acetone, soluble in isopropanol and ethanol, and very slightly soluble in water. The molecular formula is $C_{30}H_{32}F_6N_4O$ with a molecular weight of 578.61. Its CAS number is 290297-26-6

Palonosetron HCl is (3aS)-2-[(S)-1-azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline hydrochloride. It is a white to off-white crystalline powder that is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol. The molecular formula is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Its CAS number is 135729-61-2.

B. Pharmacology of Netupitant

1. Receptor Binding Studies (Study #1006030, NETU 10-24, NETU 10-16)

Receptor binding studies were conducted with netupitant, since it is a new molecular entity. Binding studies were not conducted with palonosetron, since it was established that palonosetron is a selective 5HT₃ antagonist when the drug was first approved by FDA in 2003.

Study Design and Results

Netupitant was tested at 0.10 and 10 μ M for affinity at 50 receptor sites. In these tests, it was shown that netupitant is a high affinity neurokinin (NK) 1 receptor ligand, with a pK_i 9.0 (data were not converted to K_i values). Netupitant also has lower affinity for NK2 (pK_i 5.8) and NK3 (pK_i 7.5) receptors. In addition, netupitant has > 50% inhibition at histamine H₂ (95%), adenosine A₃ (78%), dopamine transporter (DAT; 67%), L-type Ca²⁺ channel (75-100%) and muscarinic M₁ (52%) sites. The percent inhibition data for these sites were not converted to pK_i or K_i values.

In contrast to the high affinity that netupitant has for NK receptors, it does not have significant affinity (> 50% inhibition) for other CNS sites, including: opioid (μ , kappa and delta), GABA (GABA-A and GABA-B), acetylcholine nicotinic, serotonin 5HT₄, histamine (H₁, H₃), monoamine transporters (serotonin and norepinephrine), glycine, and the potassium channel. However, it is notable that the Sponsor did not assess netupitant at other CNS sites that are associated with abuse potential, such as dopamine sites, glutamate sites, cannabinoid sites, and serotonin 5HT₂ sites.

Conclusions

Although netupitant has high affinity at NK-1 receptors, it also produces > 50% inhibition at two sites associated with scheduled drugs of abuse (DAT and calcium channels). Since the data for DAT and calcium channel were not converted to pKi or Ki values, it is not clear whether activity at these sites might affect the abuse potential of netupitant. In addition, the lack of information on the affinity of netupitant at other receptors known to be associated with abuse potential (dopamine, glutamate, cannabinoid and 5HT₂) makes this receptor binding profile incomplete.

2. Preclinical Behavioral Studies

a. Behavioral Observations in Rat and Beagle Dog Toxicology Studies (Study #NETU 07-21, 07-22, 07-19, 07-18)

Four toxicology studies were conducted in which animal behavior was monitored following administration of either the combination of netupitant and palonosetron (13 week study in rats and in beagle dogs) or netupitant alone (26 week study in rats and 9 month study in beagle dogs). Each of these studies had an 8 week monitored recovery period. The doses selected were based on evaluating a full toxicological range of doses. These studies show that netupitant (alone or with palonosetron) produces only limited behavioral changes, either during drug administration or following drug discontinuation.

13-Week Rat Study with Netupitant and Palonosetron (with 8 week recovery)

Rats (n = 10 males and females/group) were given oral netupitant and palonosetron for 13 weeks, followed by an 8-week recovery period (n = 5 males and females). The dosing groups were as follows:

- 0 mg/kg (control)
- 1 mg/kg Netupitant and 2 mg/kg Palonosetron
- 3 mg/kg Netupitant and 6 mg/kg Palonosetron
- 10 mg/kg Netupitant and 18 mg/kg Palonosetron
- 18 mg/kg Palonosetron alone
- 10 mg/kg Netupitant alone

Behavioral observations included: daily clinical signs and weekly evaluation of body weight and food consumption.

During the treatment period, increased salivation was noted in a large number of males and females that received the high dose 10 mg/kg netupitant and 18 mg/kg palonosetron dose combination. This may be due to palonosetron, since a comparable incidence of salivation was noted in both sexes that received palonosetron alone. There were no other behavioral observations or changes in body weight or food consumption.

During the recovery period there were no behavioral observations or changes in body weight or food consumption.

13-Week Beagle Dog Study with Netupitant and Palonosetron (with 8 week recovery)

Beagle dogs (n = 4 males and females/group) were given oral netupitant and palonosetron for 13 weeks, followed by an 8-week recovery period (n = 2 males and females). The dosing groups were as follows:

- 0 mg/kg (controls)
- 1 mg/kg Netupitant and 3 mg/kg Palonosetron
- 3 mg/kg Netupitant and 5 mg/kg Palonosetron
- 10 mg/kg Netupitant and 10 mg/kg Palonosetron

Behavioral observations included: daily clinical signs and weekly evaluation of body weight and food consumption.

During the treatment period, salivation (moderate to severe) and shaking of the head were frequently noted in males and females in dogs that received 10 mg/kg netupitant and 10 mg/kg palonosetron. Body weight gain was significantly reduced in females that received 10 mg/kg netupitant and 10 mg/kg palonosetron during Weeks 6-13 of treatment.

During recovery, there was a decrease in body weight and body weight gain in females that received 10 mg/kg netupitant and 10 mg/kg palonosetron, but this was observed in the two dogs that were already the smallest ones in the group. There were no other changes in female dogs that received lower doses or in males at the highest dose.

6.5-Month (26-Week) Rat Study with Netupitant Alone (with 8 week recovery)

Rats (n = 20 males and females/group) were given oral netupitant alone (1, 3, and 10 mg/kg) for 6.5 months (26 weeks), followed by an 8-week recovery period (n = 10 males and females). Behavioral observations included daily clinical signs and weekly evaluation of body weight and food consumption.

During the observation period, there were no clinical signs of toxicity or other behaviors noted.

During treatment, there was reduced body weight gain in females treated that received the 10 mg/kg dose started at Week 4. However, in the same female animals, there was reduced food consumption only during the first half of the treatment period. During the recovery period, the body weights of these female animals returned to control values.

During the recovery period, there was an increase in food consumption for females.

9-Month (36-Week) Beagle Dog Study with Netupitant Alone (with 8 week recovery)

Beagle dogs (n = 4/each male and female/group) received oral vehicle, 1, 3 or 10 mg/kg netupitant alone for 9 months, followed by an 8-week recovery period (n = 3/group for vehicle and 10 mg/kg netupitant). Behavioral observations included daily clinical signs and weekly evaluation of body weight and food consumption.

During the treatment period, there were no behavioral changes. There was a decrease in body weight gain in males at 10 mg/kg in Weeks 4-5, in females at 10 mg/kg up to Week 6 and in Weeks 17 and 23-27.

During the recovery period, there were no changes in behavior or body weight.

b. Irwin Screen with Netupitant (Study #1006030)

Study Design

Male Wistar rats (n = 3/dose) received a single oral dose of netupitant at 100, 300 or 1000 mg/kg prior to observation using the Irwin screen. The animals were observed using a standard Irwin screen protocol at 1, 3 and 6 hours after dosing.

Observations included: occurrence of vocalization, stereotypies, aggressiveness, abnormal gait, Straub tail, tremor, twitches, convulsions, body posture, sedation, catalepsy, ptosis, exophthalmos, salivation, lacrimation, piloerection, abnormal respiration, defecation, urination and death; increase or decrease of spontaneous activity, touch response, body tonus and pupil size; increase of sniffing, grooming, scratching and rearing; decreased pinna reflex, traction response and grip strength and any additional observed behaviors.

Results

There were no unusual behaviors after the 100 mg/kg dose. At 1, 3 and 6 hours following oral administration of netupitant, animals showed difficulty in breathing at 300 mg/kg (2 of 3 animals) and 1000 mg/kg (3 of 3 animals). There was no effect on gait, reflexes or other neurological signs. Body weight and food and water intake were reduced at all dose levels, with body weight being markedly reduced at 24 hour mark following oral administration of the 300 and 1000 mg/kg dose. At the highest dose, one of three rats had trouble breathing and was later found dead.

Conclusions

There were no abuse-related behavioral observations following administration of netupitant.

c. Drug Discrimination Study (Study #NETU 11-25)

The drug discrimination study in animals is a pivotal animal behavioral study for abuse potential assessment and is reviewed in detail. The Sponsor conducted two drug discrimination studies in which netupitant was tested either for its ability to generalize to a benzodiazepine (a Schedule IV sedative) or MDMA (a Schedule I stimulant).

Study Design

This study used olive baboons (N=3) that had been trained to discriminate either a benzodiazepine or MDMA from vehicle. For the benzodiazepine condition, baboons had been previously trained to discriminate 1.8 mg/kg lorazepam p.o. (n = 3) or 1.8 mg/kg diazepam p.o. (n = 1) from vehicle. For the MDMA condition, baboons (n = 3) had been trained to discriminate either 1.8 or 3.2 mg/kg MDMA p.o. from vehicle (n = 2 and n = 1, respectively). The daily 20-min training sessions began 60 minutes after oral dosing with the training drug or vehicle. The fixed ratio (FR) schedule of reinforcement varied between animals, based on the number of responses that best maintained performance of that animal (ranging from FR 20-30). Criterion performance was defined as 95% stimulus-appropriate lever responses in four consecutive training sessions (two each for drug or vehicle).

Baboons were tested with vehicle and with the training dose of the training drug to verify drug stimulus control prior to the initiation of test sessions with netupitant + palonosetron. The netupitant + palonosetron doses (mg/kg, p.o.) were, respectively: 3.0/0.005, 8.0/0.013, 10.0/0.020, 13.3/0.025, 18.0/0.030. The Sponsor states that the test doses and testing times were selected based on the results of a pharmacokinetics/pharmacodynamics study.

Results

In benzodiazepine-trained baboons, all 5 doses levels of netupitant + palonosetron produced responding in all animals that was almost exclusively on the vehicle-associated lever (e.g., <5% on the drug-associated lever).

In the MDMA-trained baboons, all 5 doses levels of netupitant+ palonosetron produced responding in two of three animals almost exclusively on the vehicle-associated lever (e.g., <5% on the drug-associated lever). The third animal, however, showed full generalization to MDMA (>80% responding on the MDMA-associated lever) at the highest dose of netupitant + palonosetron (18.0/0.030 mg/kg, respectively). The investigator then re-tested all three baboons at this highest dose and all of the animals responded exclusively on the vehicle lever.

Conclusions

Netupitant + palonosetron fixed combinations do not share interoceptive stimulus effects with either a benzodiazepine or MDMA. However, it is important to note that drug

discrimination is based on the premise that the pharmacological mechanism of action underlies the ability of one drug to generalize to another, based on the interoceptive cues produced by that pharmacological mechanism. Thus, given that netupitant is an NK-1 antagonist and palonosetron is a 5HT₃ antagonist, it is unlikely that this drug combination would produce an interoceptive cue similar to that of a GABA agonist (benzodiazepine) or an inhibitor of the dopamine and serotonin transporter (MDMA). Given that there are no known drugs of abuse that are NK-1 antagonists or 5HT₃ antagonists, a drug discrimination study such as this one is of little value in assessing the abuse potential of netupitant + palonosetron.

d. Self-Administration Study (Study #NETU-11-24)

The self-administration study in rats is a pivotal animal behavioral study for abuse potential assessment and is reviewed in detail. The Sponsor conducted a self-administration drug study in which netupitant was tested for its ability to induce self-administration as a measure of the rewarding property of the drug.

Study Design

Male olive baboons (n = 3) were trained to self-administer cocaine (0.32 mg/kg/infusion, i.v.). After stable cocaine self-administration was produced using a fixed ratio (FR) 160 with a 3 hour timeout between injections, animals were allowed access to netupitant + palonosetron (0.20/0.0003, 0.6/0.0010, 1.0/0.0020 mg/kg, i.v.). The Sponsor states that the test doses and testing times were selected based on the results of a pharmacokinetics/pharmacodynamics study.

Results

The number of netupitant + palonosetron infusions that were self-administered was similar to that produced by vehicle alone at all doses of the drug combination that were tested. Additionally, there were no behavioral effects observed after the first self-injection of each dose of the drug combination.

Conclusion

Netupitant + palonosetron was not self-administered and this drug combination does not appear to have rewarding or reinforcing properties.

3. Physical Dependence Studies in Animals

The Sponsor conducted five physical dependence studies with netupitant: two toxicological studies each in rats and beagle dogs, and one dedicated physical dependence study in olive baboons.

a. Physical Dependence Assessments in Rat and Beagle Dog Toxicology Studies (Study #NETU 07-21, 07-22, 07-19, 07-18)

As described above in Section B.2.a (Preclinical Behavioral Studies), four toxicology studies were conducted in which behavior was monitored for 8 weeks after drug discontinuation, following administration of either the combination of palonosetron and netupitant (13 week study in rats and in beagle dogs) or netupitant alone (26 week study in rats and 9 month study in beagle dogs). None of the animals in any of these studies showed any behaviors during the recovery period indicative of physical dependence. Thus, netupitant, either alone or in combination with palonosetron, does not appear to induce physical dependence.

b. Physical Dependence Study in Baboons (Study #NETU-11-26)

Study Design

Male olive baboons (n = 4) received 14 days of vehicle (i.g.) with 15 minutes of behavioral observations per day to establish a baseline, followed by netupitant + palonosetron at 10.0/0.020 mg/kg (i.g.), for 30 days. Since netupitant + palonosetron will be used chronically in cancer patients, the 30-day exposure to these drugs is appropriate for investigating physical dependence. The Sponsor states that the test doses and testing times were selected based on the results of a pharmacokinetics/ pharmacodynamics study. During the first 15 days of netupitant treatment, as well as the last 5 days of treatment, animals were observed daily for 60 minutes after drug administration to evaluate overt behaviors. At the conclusion of the drug administration period, animals received 14 days of vehicle administration, immediately followed by 15 minutes of observation. Under all conditions, the opportunity to respond for food was available 20 hours/day using a FR10 schedule of reinforcement.

Following the behavioral observations, animals performed a fine motor coordination task in which an investigator presented a raisin in each of six cups, and the baboon was given 2 minutes to retrieve all of them. The following were recorded: time (seconds) taken to retrieve the treats; whether any treats were dropped; and whether an animal displayed ataxia or other unusual signs.

Animals also received a physical examination with ketamine sedation (dose and route not provided) on the following occasions: a) in between the vehicle sessions and the initiation of the netupitant sessions, b) on Day 15 or 16 of netupitant administration, c) on Day 29 or 30 of netupitant administration, d) at the conclusion of the drug discontinuation sessions.

A withdrawal score was calculated for each of the first 14 days of drug discontinuation, based on 1 point assigned for each of the 9 behaviors listed below. The behaviors assessed were:

- Number of pellets consumed in 20 hour decreased
- Time to complete raisin task increased
- One or more of the following postures increased: lying down, head lower than torso, withdrawn and/or instances of eyes being closed
- Locomotion increased or decreased
- Self-directed behaviors increased (nose rub, nose wipe, scratching, grooming, wet dog shake, masturbation)
- Aggression increased
- Tremor, jerk or rigidly braced posture increased
- Nausea or vomiting increased
- Seizure occurred

If the score contained any one of the following signs, the withdrawal for that day was considered “moderate”: tremor/jerk/rigidly-braced posture, or nausea and vomiting.

Occurrence of a seizure would result in characterization as “severe.” All other signs generally were considered indicative of a “mild” withdrawal.

Additionally, given the long half-life of the drug combination, alterations in feeding behavior were monitored for a total of 30 days after drug discontinuation, as an indicator of physical dependence.

Results

A withdrawal score was calculated for each day across the first 14 days of the drug withdrawal period. Animals received a point for each of the nine behaviors observed, but only if the frequency of the behavior was statistically significantly different (using a z score, which conveys information about where a response falls along a normal distribution, in terms of standard deviations from the mean) from baseline and behaviors observed during the end of drug administration period.

Out of a maximum possible score of 9, the daily scores for each of the 4 animals ranged from 0-3 across the entire 14 days drug discontinuation period (see below). All behaviors were characterized as “mild”.

Individual Baboon Daily Score Range:

KR	score = 0-1	Day 2 - lying down Day 3 - self-directed (nose rub)
MC	score = 0-1	Days 5 and 8 - withdrawn posture
SK	score = 0-1	Day 1 - low pellets Day 7 - high self-directed (grooming); Day 13 - longer to do raisin task

observations at 0.5, 1, 2, 4, 6, 8, 24, and 48 hours. Plasma levels of netupitant were dose-dependent, with a Tmax at 4 hours and levels remaining high for 8 hours. The Cmax was ~100 ng/ml in all baboons at doses of 10 mg/kg.

None of the tested doses of netupitant + palonosetron produced overt behavioral effects in baboons across the 24-hour observation period. This is similar to the results observed in the rat and beagle dog toxicity tests, where no overt behaviors were observed.

b. Metabolite profile of netupitant and palonosetron

The baboon pharmacokinetic study with netupitant shows that there are 3 active metabolites (>10% of parent): the desmethyl derivative, M1; the N-oxide derivative, M2; the OH-methyl derivative, M3. The three metabolites have activity as NK-1 antagonists, similar to the parent, netupitant. Palonosetron does not produce active metabolites (>10% of parent). This metabolite profile is similar to that observed in humans (see below).

2. Human Pharmacokinetics

a. Pharmacokinetics of netupitant

In humans, the proposed therapeutic dose of 300 mg oral netupitant is absorbed rapidly (Tmax = 4-5 hours). For the proposed therapeutic dose of 0.5 mg oral palonosetron, the Tmax is 3-6 hours. The elimination half-life of netupitant ranges from 30-100 hours, while the elimination half-life of palonosetron ranges from 40-50 hours. Pharmacokinetic parameters were similar in cancer patients and in healthy volunteers.

b. Metabolite profile of netupitant and palonosetron

Similar to animals, there are 3 active metabolites of netupitant have been detected in human plasma: M1, M2 and M3 (which have (respectively) 11%, 47% and 16% of the parent). All three metabolites were detectable for long periods after netupitant administration, with the following timeframes: M1 = 176-336 hours, M2 = 48-120 hours, M3 = 144-336 hours.

As shown below in Section D (Clinical Studies), there are no abuse-related signals associated with administration of netupitant in humans, so there are no data suggestive that the active metabolites of netupitant produce AEs indicative of abuse potential.

In humans, as in animals, palonosetron does not produce any major metabolites (>10% of the parent).

D. Clinical Studies

The following information was culled from Sponsor summaries of clinical studies submitted in the NDA. A total of 3592 individuals participated in Phase 1, 2 and 3 studies in which netupitant alone or netupitant + palonosetron was administered.

Phase 1 studies were conducted in healthy volunteers who were exposed to oral netupitant alone (10 studies) or to oral netupitant in combination with palonosetron (10 studies). The doses of netupitant in Phase 1 studies ranged from 10 to 450 mg. Notably, a human abuse potential study with netupitant + palonosetron was not deemed necessary by CSS during drug development, given that preclinical abuse-related studies (general behavioral studies, self-administration study, and drug discrimination study) showed that this drug combination produced no abuse-related signals. Phase 2/3 studies (a total of 4 studies) tested netupitant at doses of 100, 200 and 300 mg, with netupitant administered alone or in combination with palonosetron.

Although all AEs were evaluated during clinical studies with netupitant, Standardized MedDRA Queries (SMQs) were selected *a priori* to evaluate CNS and psychiatric effects that might reflect abuse-related events. These included euphoric mood, anxiety, insomnia, sleep disorder, and obsessive thoughts, delirium, psychosis, and psychotic disorders.

There was only one individual who participated in any of the Phase 1 and Phase 2/3 studies with netupitant + palonosetron who reported a euphoric mood-related AE. In this single incident (1 of 3592, < 0.001%), a healthy individual reported euphoria after receiving 600 mg netupitant + 1.5 mg palonosetron in a pharmacokinetic study with moxifloxacin. Notably, the doses of netupitant and palonosetron administered to this individual were (respectively) two and three times greater than that of the proposed therapeutic doses of 300 mg netupitant and 0.5 mg palonosetron. This isolated case report is not representative of the centrally-mediated responses to netupitant and palonosetron and thus not indicative that this drug combination has abuse potential.

With all cycles of Phase 2 (n = 1418) and Phase 3 (n = 1862) studies were combined, there were 533 of the 3280 patients (16.3%) who reported CNS-related AEs, including nervous system disorders (3.3%; 108 of 3280 patients; primarily accountable by headache at 2.4% and dizziness at 2.3%) and psychiatric disorders (3.2%; 106 of 3280 patients; primarily accountable by insomnia at 2.1%). There were no reports of euphoria-related AEs.

When the multicycle Phase 3 trials (testing 300 mg netupitant + 0.5 mg palonosetron) were analyzed separately from the combined Phase 2/3 trials, 362 of 1862 patients (19.4%) reported CNS-related AEs of interest. As with the Phase 2/3 population, the AEs of highest frequency were psychiatric disorders (4.8%, primarily accountable by insomnia at 3.3%), and nervous system disorders (4.5%, primarily accountable by headache at 2.4% and dizziness at 3.3%). There were no reports of euphoria-related AEs.

Conclusion:

In both Phase 1 and Phase 2/3 clinical studies with netupitant, and with netupitant + palonosetron, there were only isolated abuse-related signals and only a single report of euphoria. Thus, there does not appear to be any abuse potential associated with netupitant, or with netupitant + palonosetron, when it is administered to humans.

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/s/

KATHERINE R BONSON
05/30/2014

SILVIA N CALDERON
05/30/2014

MICHAEL KLEIN
05/30/2014

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 29, 2014

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Error Products
(DGIEP) Office of Drug Evaluation III
Office of New Drugs

FROM: Michael F. Skelly, Ph.D., Pharmacologist
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs covering NDA 205-718, Akynzeo
(Netupitant and Palonosetron HCl combination capsule),
sponsored by Helsinn Healthcare

At the request of the Division of Gastroenterology and Inborn Error Products (DGIEP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence study:

Study Number: NETU-09-07
Study Title: "Bioequivalence study of a new netupitant/
palonosetron fixed combination (300 mg/0.50 mg)
versus extemporaneous combination of netupitant
300 mg and palonosetron 0.50 mg after single
dose administration to healthy male and female
volunteers"

The inspection of the clinical portion was conducted by Alexandra B. Pitkin (ORA Investigator, LOS-DO) at Cross Research S.A., in Arzo, Switzerland, from April 28 to May 2, 2014. There were no objectionable findings during the inspection and Form FDA-483 was not issued. The inspection of the analytical portion was conducted by [REDACTED] (b) (4)

[REDACTED] (b) (4) There were no objectionable findings during the inspection and Form FDA-483 was not issued.

During the 2008 inspection of study PALO-06-16 for palonosetron NDA 22-233, we raised the possibility of *ex vivo* reduction of palonosetron N-oxide (M9) back to palonosetron, as discussed in technical publications on other N-oxide drug metabolites, and in Helsinn's patents on netupitant N-oxide (M2) as a drug alone or in combination with palonosetron. Since then, [REDACTED] (b) (4) demonstrated that the N-oxide metabolites of palonosetron and netupitant are sufficiently stable *ex vivo* that their reduction back to the parent amine drugs, during storage and handling of plasma samples, does not interfere with measurement of the parent amine drugs in plasma.

Conclusion:

Following review of the inspectional findings, I recommend that:

- The results from the clinical and bioanalytical portions of study NETU-09-07 are acceptable for Agency review.

Michael F. Skelly, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

**Cross Research S.A., Arzo, Switzerland - NAI
(FEI# 3008374644)**

[REDACTED] (b) (4) - NAI

Page 3 - NDA 205-718, Akynzeo (Netupitant and Palonosetron HCl combination capsule), sponsored by Helsinn Healthcare

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Dejernet/CF

OSI/DBGLPC/BeB/Haidar/Choi/Skelly

OSI/DBGLPC/GLPB/Bonapace/Dasgupta

CDER/OND/ODEIII/DGIEP/Chung

CDER/OND/OCP/Noory

ORA/LOS-DO/Pitkin

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MICHAEL F SKELLY
05/29/2014

SAM H HAIDAR
05/29/2014

WILLIAM H TAYLOR
05/30/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Consult Request Date: October 8, 2013

From: Erica Radden, M.D.
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne Yao, M.D., OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Gastroenterology and Inborn Errors Products
(DGIEP)

Drug: Akynzeo (netupitant/palonosetron HCl)

Application Number: NDA 205718 (IND 73,493)

Re: Review of the Pediatric Plan

Sponsor: Helsinn Healthcare SA

Proposed Indication: For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy and moderately emetogenic cancer chemotherapy.

Proposed Dosage form and Route of administration: fixed dose combination capsule of palonosetron 0.5 mg and netupitant 300 mg; oral

Proposed Dosing regimen: single oral dose one hour prior to highly and moderately emetogenic chemotherapy

Consult Request: DGIEP requests assistance from the Pediatric and Maternal Health Staff (PMHS) in evaluating the sponsor's Pediatric Plan.

Materials Reviewed:

- Palonosetron HCl and Netupitant Fixed-Dose Combination Capsule Background Package, (March 15, 2013)
- FDA's request for a Pediatric Plan for netupitant/palonosetron, NDA 205718 (March 12, 2014)
- Sponsor's response to FDA's request (March 12, 2014) for a Pediatric Plan for netupitant/palonosetron, NDA 205718 (March 26, 2013)
- Sponsor's revised Pediatric Plan for netupitant/palonosetron, NDA 205718 (April 4, 2014)
- Prior PMHS consult review for netupitant/palonosetron IND 73493 (May 13, 2013)

Background:

Akynzeo (netupitant/palonosetron hydrochloride) is fixed dose combination capsule comprised of netupitant, a substance P/neurokinin 1 (NK1) antagonist, and palonosetron hydrochloride, a serotonin subtype 3 (5-HT₃) receptor antagonist. The proposed indication is prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy and moderately emetogenic cancer chemotherapy.

Reviewer comment: Nausea and vomiting associated with initial and repeat courses of cancer chemotherapies will be referred to as CINV.

Regulatory Background:

The sponsor submitted an NDA for an oral formulation of netupitant/palonosetron fixed dose combination (FDC) on September 27, 2013. Despite advice at the pre-NDA meeting held on April 16, 2013, that a (b) (4) would not likely be granted for pediatric studies, the NDA submission contained a request for a (b) (4). The (b) (4) request was based on (b) (4).

Although the Division advised the sponsor on March 12, 2014, that a (b) (4) would not be granted and requested submission of a revised Pediatric Plan, the sponsor submitted a letter further reiterating their reasons for requesting a (b) (4). Consequently, a teleconference was held between the sponsor, the Division and PMHS on April 28, 2014, in which the Agency's position was clarified. The sponsor was advised that they would need to attempt to develop an age-appropriate formulation, (which could include formulations other than oral) and submit a pediatric plan detailing the studies they propose to conduct to address PREA along with a timeline. Accordingly, the sponsor submitted a pediatric plan on April 4, 2014. DGIEP requested PMHS' assistance with review of the application (see the prior PMHS consult review for netupitant/palonosetron, IND 73493, dated May 13, 2013 [DARRTS reference ID: 3307725], for further regulatory background information).

Sponsor's Pediatric Plan:

The sponsor proposes to conduct three juvenile toxicity studies in rats and dogs:

(b) (4)

At the same time the sponsor plans to initiate these non-clinical studies, the sponsor plans to begin development of an age-appropriate formulation for pharmacokinetic/pharmacodynamic (PK/PD) studies. To support the initial pediatric PK/PD clinical study, the sponsor proposes to develop an age-appropriate formulation of netupitant (as a single agent) to be used with palonosetron. The sponsor plans to first develop a single-agent oral liquid formulation of netupitant for patients birth to <18 years of age, which would be given with palonosetron¹ orally. If the sponsor is unable to develop an oral liquid netupitant formulation, the sponsor proposes to develop an oral solid netupitant formulation for patients 6 to <17 years of age using age-appropriate dosage strengths based on body weight ranges. An IV formulation of netupitant will be developed for use in combination with the IV formulation of palonosetron for use in patients ≤6 years of age. (b) (4)

If no oral formulation can be developed (liquid or solid) for use in pediatric patients down to 6 years of age, then this proposed (b) (4) (b) (4) formulation would be used for all pediatric age groups for the initial PK/PD study, and would be administered concomitantly with IV palonosetron via separate IV injections. Use of the (b) (4) formulation (currently under development) in pediatric patients would be contingent upon demonstration of safety and effectiveness in adults in planned adult clinical studies. Based on the contingencies of the development of an age-appropriate formulation for the initial PK/PD study and outcomes of the pediatric PK/PD clinical trial, a final (oral or IV) pediatric age-appropriate combination formulation would be developed and used in a pediatric safety and efficacy trial.

Reviewer comment: The Office of the Chief Counsel was consulted regarding the use of a netupitant (b) (4) to address PREA for netupitant/palonosetron. Based on their feedback, if the sponsor cannot develop an age appropriate formulation of the combination of netupitant (and not the netupitant (b) (4)) and palonosetron, then there would be no pediatric formulation of netupitant/palonosetron with which to label any data derived from studies with the netupitant (b) (4). Consequently, the development of the (b) (4) could not be compelled under PREA. Additionally, if we agree that the sponsor has made reasonable attempts to develop an age-appropriate combination product of netupitant/palonosetron and is unsuccessful, then a partial waiver may be granted in the age group that is unable to use the existing formulation. In order to obtain the waiver, the sponsor would need to provide data to support this claim for review by the Division and PeRC which would be publicly

¹ The "oral" formulation of palonosetron that the sponsor proposes to study with netupitant is, in fact, the IV formulation which will be given orally. This is similar to the agreed upon administration of palonosetron in the studies being performed under WR for palonosetron, NDA 21372.

posted. Notably, only one product thus far has qualified for a waiver for this reason (Vimovo [naproxen/esomeprazole magnesium], NDA 22511). A future NDA submission of the any (b) (4) formulation (as a new active ingredient, new dosage form, and potentially new dosage regimen) would trigger PREA, however.

The proposed clinical studies consist of:

- (1) an initial PK/PD pediatric trial of single dose netupitant given concomitantly (in separate formulations) with single dose palonosetron
- (2) a pediatric clinical efficacy and safety trial of the netupitant/palonosetron FDC compared to standard therapy in pediatric cancer patients 0-17 years of age undergoing treatment with emetogenic chemotherapy.

For the safety and efficacy trial, the sponsor plans to conduct either an add-on superiority trial of netupitant/palonosetron FDC compared to palonosetron, or a non-inferiority study of the FDC compared to aprepitant used with a 5HT₃ receptor antagonist. The active comparator will be determined based on the standard of care for the treatment of the pediatric cancer population at the time of protocol preparation.

Comments on the Pediatric Research Equity Act (PREA) and the Pediatric Plan:

Under PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. PREA is triggered by this new ingredient. The sponsor proposes to conduct studies in all pediatric age groups (b) (4). However, the sponsor should be advised that if they are unable to develop an age-appropriate formulation of the netupitant/palonosetron combination without the use of a netupitant (b) (4), they would be eligible for a partial waiver of studies in the pediatric populations for which an age-appropriate formulation could not be developed.

Additionally, the non-clinical reviewers have determined that only a single 8-week juvenile toxicity study in rats is required which does not need to be completed prior to the initiation of pediatric clinical trials. Therefore, the sponsor's proposed studies in non-clinical section should be replaced with this required study. Furthermore, based on these recommended revisions to the pediatric development plan regarding formulation development and nonclinical study requirements, the timeline for the pediatric development plan should be revised accordingly to initiate clinical studies sooner.

PMHS reviewed the background materials and provided input on the proposed pediatric plan, in addition to assisting in preparation for the Pediatric Review Committee (PeRC) meeting on May 14, 2014. PMHS participated in the internal meetings from October, 2013 to April, 2014; the PeRC preparation meeting on April 14, 2014; and the sponsor teleconference on March 28, 2014. PMHS also plans to participate in the additional internal meetings scheduled through June, 2014. Our input will be reflected in the approval letter.

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/s/

ERICA D RADDEN
05/21/2014

HARI C SACHS
05/22/2014
I agree with these recommendations.

LYNNE P YAO
05/23/2014

INTRODUCTION

On September 26, 2013, Helsinn Healthcare submitted NDA 205-718 for Netupitant and Palonosetron HCL fixed dose combination capsule for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. The proprietary name AKYNZEO[®] was conditionally accepted for this combination drug product on December 13, 2013.

Palonosetron, a serotonin subtype 3 (5HT₃) antagonist, was initially approved on July 25, 2003, as an injectable formulation and is marketed as Aloxi[®] (NDA 21-372). A capsule formulation of Aloxi[®] (palonosetron) was subsequently approved on August 22, 2008 (NDA 22-233); however, the product was withdrawn from marketing on September 4, 2012, for reasons not related to safety of effectiveness.¹ Netupitant is a Neurokinin 1 (NK1) antagonist.

DGIEP consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the Akynzeo labeling.

This review provides recommended revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Palonosetron

Palonosetron² is a 5-HT₃ receptor antagonist indicated for:

- Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses
- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated

Netupitant

Netupitant is an NK₁ receptor antagonist. Netupitant is being developed for use in combination with palonosetron for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including highly emetogenic chemotherapy.³

Chemotherapy-induced nausea and vomiting (CINV)

Nausea and vomiting is a common side effect associated with the administration of chemotherapeutic drugs. Nausea and vomiting can cause weight changes, dehydration, electrolyte imbalances and fatigue.⁴ Although nausea and vomiting are related they are also

¹ <https://www.federalregister.gov/articles/2012/09/04/2012-21652/determination-that-aloxi-palonosetron-hydrochloride-capsules-05-milligram-base-were-not-withdrawn>

² Approved package insert for Aloxi[®] (palonosetron hydrochloride), February 6, 2014.

³ Stathis, M., Pietra, C., Rojas, C., Slusher, B. (2012). Inhibition of substance P-mediated responses in NG108-15 cells by netupitant and palonosetron exhibit synergistic effects. *European Journal of Pharmacology*, 689, 25-30.

⁴ Navari, R. (2013). Management of Chemotherapy-Induced Nausea and Vomiting. *Drugs*, 73:249–262. doi: 10.1007/s40265-013-0019-1

separate events and often one is treated without the other. Females who experienced severe emesis during pregnancy are believed to be at greater risk for experiencing CINV.⁵

DISCUSSION

Review of Data

Pregnancy

A search of published literature was performed and no data was found with the use of palonosetron or netupitant in pregnant women. No adverse findings were noted in the animal reproduction studies conducted with palonosetron.⁶ However, evidence of developmental toxicity (i.e., external and skeletal abnormalities and reduction in fetal weight) was seen in animal reproduction studies in rabbits with netupitant.⁷

Lactation

The Drugs and Lactation Database (LactMed)⁸ was searched for available lactation data on with the use of palonosetron or netupitant, and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

⁵ Jordan, K., Sippel, C., Schmoll, H-J. (2007). Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present and Future Recommendations. *The Oncologist*, 12:1143-1150. doi: 10.1634/theoncologist.12-9-1143.

⁶ Chopra, Y. pharmacology/toxicology review for Aloxi. 7/11/2003.

⁷ See DGIEP pharmacology/toxicology review for Akynzeo.

⁸ United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

CONCLUSION

Based on a lack of human pregnancy data and adverse embryo-fetal findings in animals, PMHS recommends that Akynzeo be classified as a Pregnancy Category C drug.⁹

The pregnancy subsection of the labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. PMHS-MHT deleted the sponsor's proposed

(b) (4)
The labeling regulations allow omission of inapplicable subsections (see 21 CFR 201.56(d)(4)). Any relevant Akynzeo (b) (4) would have been placed in subsection 8.1 Pregnancy in proposed PLLR format. The nursing mothers subsection of labeling was revised to comply with current labeling recommendations.

PMHS-MHT discussed our labeling recommendations with DGIEP at a meeting on April 24, 2014. PMHS-MHT and the DGIEP Pharmacology/Toxicology team recommendations are below and reflect the discussions with DGIEP at that meeting. PMHS-MHT refers to the NDA action for final labeling. The sponsors draft labeling recommendation can be found in Appendix A.

LABELING RECOMMENDATIONS

8 USE IN SPECIFIC POPULATIONS

8.1. Pregnancy Pregnancy Category C

Risk Summary

Adequate and well-controlled studies with AKYNZEO have not been conducted in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed following daily administration of netupitant in pregnant rats during the period of organogenesis at doses up to (b) (4) times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy. However, a dose-dependent increase in adverse effects on embryo-fetal development was observed following daily administration of netupitant in pregnant rabbits during the period of organogenesis with doses at least (b) (4) times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy. Daily administration of netupitant in rats up to (b) (4) times the human AUC at the recommended human dose during organogenesis through lactation produced no adverse effects in the offspring. In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed following oral administration during the period of organogenesis at doses up to 921 and 1841 times the recommended human oral dose in rats and rabbits, respectively. AKYNZEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

⁹ Pregnancy Category C Definition: Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well controlled studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no adequate and well controlled studies in humans.

Animal Data

Daily administration of up to 30 mg/kg netupitant in rats (^{(b) (4)} times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy) during the period of organogenesis produced no effects on embryo-fetal development. However, an increased incidence of external and skeletal abnormalities in rabbit fetuses was observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher ^{(b) (4)} times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy) during the period of organogenesis. These abnormalities included positional abnormalities in the limbs and paws, and fused sternebrae. Reduction in fetal rabbit weight occurred at 30 mg/kg/day. Maternal toxicity in rabbits (i.e. loss of bodyweight during the treatment period) was also observed at 30 mg/kg/day. Daily administration of up to 30 mg/kg netupitant ^{(b) (4)} times the human AUC at the recommended human dose) in rats during organogenesis through lactation produced no adverse effects in the offspring.

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed in pregnant rats given oral doses up to 60 mg/kg/day (921 times the recommended human oral dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (1841 times the recommended human oral dose based on body surface area) during the period of organogenesis.

8.3 Nursing Mothers

It is not known whether AKYNZEO is present in human milk. Because many drugs are present in human milk and because of the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study [see Non-Clinical Toxicology (13.1)], a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Appendix A Sponsors Recommendations

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

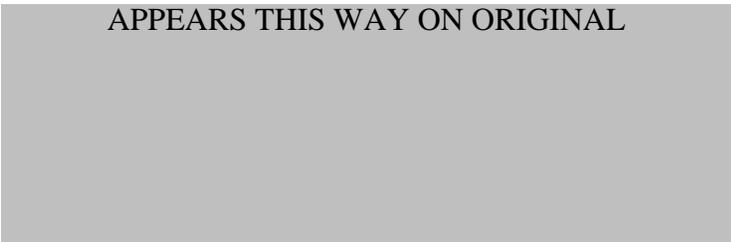
(b) (4)

8.3 Nursing Mothers

It is not known whether palonosetron and netupitant, the two components of AKYNZEO, are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for ^{(b) (4)} tumorigenicity

shown for palonosetron in the rat carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

APPEARS THIS WAY ON ORIGINAL



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/s/

CARRIE M CERESA
05/16/2014

JEANINE A BEST
05/16/2014

LYNNE P YAO
05/21/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 12, 2014

TO: Mary Chung, Pharm.D., Regulatory Project Manager
Nancy Snow, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205718

APPLICANT: Helsinn Healthcare SA

DRUG: Akynzeo[®] (Netupitant Palonosetron Fixed Dose Combination)
NME: Yes
THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) and highly emetogenic cancer chemotherapy (HEC)

CONSULTATION REQUEST DATE: November 8, 2013
INSPECTION SUMMARY GOAL DATE: May 16, 2014
DIVISION ACTION GOAL DATE: September 16, 2014
PDUFA DATE: September 16, 2014

I. BACKGROUND:

The sponsor, Helsinn Healthcare SA, submitted this NDA for the netupitant and palonosetron HCl Fixed-Dose Combination Capsule (FDC) for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy (MEC and HEC). Netupitant is a novel selective NK1 receptor antagonist. Palonosetron is a selective 5-HT₃ receptor antagonist that was approved in the US in 2003 in a formulation for intravenous use and in 2008 in an oral formulation. Netupitant is a new molecular entity.

The sponsor submitted the following four studies in support of the application:

1. NETU-07-07 entitled “A Randomized, Double-Blind, Parallel Group, Dose-Ranging, Multicenter Study Assessing the Effect of Different Doses of Netupitant or Placebo Administered with Palonosetron and Dexamethasone on the Prevention of Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting in Cancer Patients”
2. NETU-08-18 entitled “A phase III multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group study of the efficacy and safety of oral netupitant administered in combination with palonosetron and dexamethasone compared to oral palonosetron and dexamethasone for the prevention of nausea and vomiting in cancer patients receiving moderately emetogenic chemotherapy”
3. NETU-10-29 entitled “A phase III, multicenter, randomized, double-blind, unbalanced (3:1) active control study to assess the safety and describe the efficacy of netupitant and palonosetron for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles”
4. Palo-10-01 entitled “Single-dose, multicenter, randomized, double-blind, double-dummy, parallel group study to assess the efficacy and safety of oral palonosetron 0.50 mg compared to I.V. palonosetron 0.25 mg administered with dexamethasone for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving highly emetogenic cisplatin-based chemotherapy”

Protocol NETU-07-07 was a multicenter, randomized, active-controlled trial with four principal arms comparing three different doses of oral netupitant combined with oral palonosetron and oral dexamethasone against oral palonosetron and oral dexamethasone (control group). An additional arm with aprepitant administered with ondansetron and dexamethasone was included for exploratory purposes only. The primary efficacy endpoint was the complete response rate (CR) defined as no emetic episodes and no rescue medication, within 120 hours after the start of the highly emetogenic chemotherapy administration. The study was conducted as a Phase 2 study from February 2008 to November 2008 at 44 sites in the Ukraine and Russia and enrolled a total of 694 subjects. According to the clinical study report submitted by the sponsor, the percent of patients with complete response over 0-120 hours after start of cisplatin administration was 76.5% in the palonosetron alone group and 87.4%, 87.6%, and 89.6% in the netupitant 100 mg, 200 mg, and 300 mg groups, respectively. Differences from palonosetron alone were greater than 10% (10.9% to 13.2%). All doses of netupitant were statistically superior to palonosetron alone ($p \leq 0.018$). This was designed and conducted as a Phase 2 study. In a meeting on June 18, 2010, the division agreed that NETU-07-07 would be acceptable as the lone trial to support the fixed dose combination capsule for the prevention of acute and delayed HEC-CINV, provided review of the data support efficacy and safety.

Protocol NETU-08-18 was a Phase III, multicenter, multinational, randomized, double-blind, double-dummy, parallel group, stratified study. It was designed to assess both acute and delayed MEC. The primary evaluation was the proportion of patients with CR (defined as no emesis, no rescue medication) in the delayed phase (time interval 25-120 hours after the start of the MEC administration) at cycle 1. The study was conducted between April 2011 and November 2012 at 177 study centers in 15 countries and enrolled a total of 1455 subjects. Efficacy evaluations were based on the patients' documentation of emetic episodes (episodes of retching or vomiting) and nausea assessed by Visual Analogue Scale (VAS) and intake of rescue medication. To collect these data, patient diary covering Days 1 to 5 at each cycle were used. According to the conclusion of the study results contained in the clinical study report submitted by the sponsor to the NDA, this study demonstrated the superiority of the netupitant/palonosetron (300 mg/0.50 mg) FDC over palonosetron alone with respect to the primary, CR in the delayed phase, and both key secondary, CR in the acute and overall phases after the administration of moderately emetogenic chemotherapy during the first chemotherapy cycle.

Protocol NETU-10-29 was a multicenter, multinational, randomized, active-controlled, double-blind, double-dummy, unbalanced (3:1), parallel group, stratified study. It was designed to assess the safety and tolerability of a single oral dose of a Fixed-Dose Combination of netupitant and palonosetron (300 mg/0.50 mg) in initial and repeated cycles of chemotherapy. The primary efficacy evaluation was the proportion of patients with CR (defined as no emesis, no rescue medication) in the delayed phase (time interval 25-120 hours after the start of the MEC administration) at cycle 1. It was conducted from July 2011 to September 2012 at 72 centers in 10 countries and randomized 413 subjects. According to the conclusion of the study

results contained in the clinical study report submitted by the sponsor to the NDA, the netupitant/palonosetron FDC combined with dexamethasone demonstrated high response rates in the prevention of nausea and vomiting, in the delayed, acute and overall phases of initial and repeated cycles of chemotherapy.

Protocol Palo-10-01 was a multicenter, multinational, randomized, active-controlled, double-blind, double-dummy study and was designed to demonstrate the non-inferiority of single dose oral palonosetron 0.50 mg versus single dose Intravenous (I.V.) palonosetron 0.25 mg in terms of percentage of patients with Complete Response (CR) during the acute phase (0-24 hours). The primary efficacy evaluation was the proportion of patients with CR (defined as no emesis, no rescue medication) within 24 hours after the start of HEC administration on Day 1. It was conducted from June 2011 to November 2012 at 80 study sites in 12 countries and enrolled a total of 743 subjects. According to the sponsor, this study demonstrated the non-inferiority of oral palonosetron 0.50 mg compared with I.V. palonosetron 0.25 mg in terms of the primary efficacy endpoint i.e. CR in the acute phase.

The review division chose sites for inspection on the basis of several factors including attempt to provide coverage for all four studies, high enrollment, inspectional history of the clinical investigator, geographical diversity and feasibility. In December 2013, when it was not possible to inspect sites in the Ukraine, two sites in India were chosen for NETU0 8-18 and NETU 10-29. Because NETU 07-07 was conducted in Ukraine and Russia only, and inspections in Russia presented difficulties with scheduling and ultimately were not feasible to inspect, it was not possible to provide more than the original Russian site inspection chosen for NETU 07-07. A sponsor inspection was conducted as per usual OSI procedures because this is a new molecular entity. In addition, the sponsor inspection evaluated noncompliance at a Russian site noted in the clinical study report for NETU 07-07 and information concerning monitoring at Ukrainian sites that could not be inspected.

II. RESULTS (by Site):

Name, Address and Type of Inspected Entity	Protocol # Site # and # of Subjects	Inspection Date	Final Classification*
CI: Dr. Tibor Csozsi Tószegi út 21, H-5004 Szolnok Hungary	NETU-08-18/ Site 5403/ 47 Subjects PALO-10-01/ Site 5405/ 45 Subjects	January 13 to 23, 2014	VAI
CI: Dr. Anna Lowczak ul. Kuracyjna 30 82-550 Prabuty, Poland	NETU-10-29/ Site 5607/ 30 Subjects	January 27 to 30, 2014	NAI
CI: Dr. Katarzyna Zajad ul. Roentgena 5 02-781 Warszawa, Poland Phone: +48.225.462.169	PALO-10-01/ Site 5602/ 37 subjects	January 20 to 24, 2014	VAI
CI: Dr. Anna V. Alyasova 2 Nizhne-Volzhszkaya Nab. 603001 Nizhny Novgorod, Russia	NETU-07-07/ Site 101/ 37 subjects	December 9 to 13, 2013	VAI
CI: Dr. Mamillapalli Gopichand #33-25-33 Venkatakrishanayya Street Suryaraopet Vijayawada 520002, India	NETU-08-18/ Site 3102/ 55 Subjects	February 10 to 14, 2014	NAI
CI: Professor Narendra Khippal S.M.S. College and Hospital Shastri Nagar, Jaipur, India, 302016	NETU-10-29/ Site 4205/ 20 Subjects	February 3 to 7, 2014	NAI
Sponsor: Helsinn Healthcare SA Via Pian Scairolo 9 Pazzallo-Lugano Switzerland	NETU-07-07 NETU-08-18 NETU-10-29 PALO-10-01	March 24 to April 4, 2014	Pending* (preliminary NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Dr. Tibor Csozsi, Szolnok, Hungary

- a. **What was inspected:** At this site, for Protocol NETU-08-18, a total of 53 subjects were screened; 47 subjects were enrolled and randomized. For Protocol Palo-10-10, a total of 48 subjects were screened; 45 subjects were enrolled and randomized. Informed consent was verified for all subjects. For Protocol NETU-08-18, an audit of 24 subjects' records was conducted. The review included subject diaries, ECGs, source records, and test article handling and accountability. For Protocol Palo-10-10 an audit of records from 10 subjects who received study drug (oral palonosetron) was conducted and the remaining 35 subjects' records (intravenous and oral treatment arms) were reviewed for diary data, chemotherapy administration, and concomitant medications data.
- b. **General Observations/Commentary:** For both studies, there was no evidence of under-reporting of adverse events and the efficacy data were verifiable. A Form FDA 483 was issued because, for Protocol Palo-10-10, concomitant medications were not recorded in the eCRF as follows:
1. The concomitant medication Mannisol was not recorded for Subjects 04, 10, 15, 16, 17, 18, 19, 22, 23, 26, 29, 30, 31, 33, 34, 37, 38, 39, 40, 42, 43, 45, 46, 47, and 48.
 2. The concomitant medication Suprastin (chloropyramine) was not recorded for Subjects 12, 20, 21, 35 and 48.
- These violations involved minor record keeping issues and should not affect study outcome. The clinical investigator responded in a letter dated February 3, 2014, promising corrective action.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Dr. Anna Lowczak, Prabuty, Poland

- a. **What was inspected:** At this site, for Protocol NETU-10-29, a total of 31 subjects were screened, 30 subjects were enrolled and 22 subjects completed the study. There was one death. The field investigator reviewed study related documents for 12 subjects. Records reviewed consisted of source documents, eCRFs and medical records. The review also included informed consent documents, inclusion/exclusion criteria, clinical laboratory values, efficacy parameters, study drug accountability, and adverse events.
- b. **General observations/commentary:** For the efficacy endpoint data, vomiting, nausea, and rescue medications, there were no discrepancies between the source data and the line listings from the NDA submission provided to the field investigator. There were no discrepancies in the timing of administration of chemotherapy relative to administration of study drug and concomitant

medications. There was no evidence of under-reporting of adverse events.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

3. Dr. Katarzyna Zajad, Warszawa, Poland

- a. **What was inspected:** At this site, for Protocol Palo-10-10, a total of 43 subjects were screened; 37 subjects were enrolled and 33 subjects completed the study. An audit of 16 subjects' records was conducted. The review included consent form documents, study correspondence, source records, and test article handling and accountability.
- b. **General observations/commentary:** A Form FDA 483 was issued because:
1. The investigation was not conducted in accordance with the investigational plan because two adverse events were not reported. Specifically, fatigue was not reported for Subject 560209 (palonosetron IV arm) and anemia during hospitalization was not reported for Subject 560210 (palonosetron IV arm).
 2. Failure to maintain adequate case histories: The patient diary for Subject 560231 (palonosetron IV arm) was not available during the inspection. According to the hospital records the subject returned the diaries and data were transcribed into the CRF, however, at the close of the study, the diary was noted to be missing and this was documented in a note to file dated December 10, 2013. The CI could not offer an explanation, but the study team was re-trained by the CI to apply increased attention to prevent the loss of source documentation in the future.

Other than Item #1, there was no evidence of under-reporting of adverse events. Except for the isolated Item #2 noted above, the efficacy data were verifiable.

Also noted at this site was the fact that the rescue medication log for this study did not include all rescue medication that was dispensed during the study and rescue medications were not returned by the patient.

Reviewer Note: Although rescue medication was to be documented in the eCRF, there was no requirement for separate rescue medication accountability logs and the investigator was authorized to use an alternative rescue medication.

- c. **Assessment of data integrity:** The violations noted on the Form FDA 483 are considered minor and do not impact data reliability. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

4. Dr. Anna V. Alyasova, Novgorod, Russia

- a. **What was inspected:** At this site, for Protocol NETU-07-07, a total of 51 subjects were screened; 37 subjects were enrolled and 37 subjects completed the study. The review included consent form documents, study correspondence, source records, and test article handling and accountability. An audit of all enrolled subjects' records was conducted for consent form document review and endpoint data verification by diary review.
- b. **General observations/commentary:** The FDA investigator reviewed 50% of enrolled subjects and found no evidence of under-reporting of AEs. The primary endpoint data were verified in 100% of enrolled subjects. Also it was verified that, in 100% of enrolled subjects, the time of drug administration was within the allowed time window (60 min±2 min) and that the time was recorded accurately in Listing 11, "Study Drug Administration—All Randomized Subjects". A Form FDA 483 was issued for failure to maintain adequate case histories. Specifically, in 3 of 26 subject diaries reviewed, a data entry error was detected in the corresponding case report form (CRF). The subject diaries for Subjects 101-1082, 101-1481, 101-1396 recorded dexamethasone tablets taken as 1 (Day 2, PM); 1 (Day 3, AM); and 3 (Day 3, AM). The corresponding CRF recorded 2 tables in each case. Each of these subjects drug accountability log reported "0" tablets returned. The discrepancies were not recorded in the protocol deviation log and were not mentioned in the monitoring visits follow-up letters.

Dr. Alyasova responded that the errors were in the subject diaries and not in the drug accountability, but that these errors were not detected at the time of entry into the CRFs. She promised corrective action in that more attention will be paid in training subjects to complete diaries and training study staff to be careful about the documentation.

- c. **Assessment of data integrity:** The violations noted on the Form FDA 483 are considered minor and do not impact data reliability. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

5. Dr. Mamillapalli Gopichand, Vijayawada 520002, India

- a. **What was inspected:** At this site, for Protocol NETU-08-18, a total of 62 subjects were screened, and 55 subjects were enrolled. Records reviewed consisted of source documents, eCRFs, and medical records. The review also included informed consent documents, inclusion/exclusion criteria, clinical laboratory values, study diaries, study drug accountability, and adverse events. The FDA field investigator reviewed 100% of subjects' records for informed consent documents and primary efficacy endpoint.

- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events, and the source data for the primary efficacy data were able to be verified at the site. No significant regulatory violations were noted, and no Form FDA 483 was issued.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

6. Professor Narendra Khippal, Jaipur, India, 302016

- a. **What was inspected:** At this site, for Protocol NETU 10-29, a total of 23 subjects were screened, and 20 subjects were enrolled. The field investigator reviewed the informed consent documents and subject diaries for efficacy endpoints for all 20 subjects. A review was conducted of 6 subjects' records for adverse events and for 13 subjects' records for eligibility criteria. The review also included study drug accountability.
- b. **General observations/commentary:** For the efficacy endpoint data, vomiting, and rescue medications, there were no discrepancies between the source data and the line listings from the NDA submission provided to the field investigator. There was no evidence of under-reporting of adverse events. No regulatory violations were noted and no Form FDA 483 was issued. There were three discussion items. Dr. Khippal failed to document his discussions with the monitor regarding the clarification of SAEs; and failed to document reasons for administration of antibiotics and the impact of potential infections on study participation; He submitted a progress report to the Ethics Committee late. Specifically, he submitted the first progress report to the Ethics Committee on July 11, 2012, instead of in March 2012 when it was due. Dr. Khippal responded verbally to each of the discussion items during the closeout of the inspection.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

7. Helsinn Healthcare SA, Pazzallo-Lugano, Switzerland

Note: Observations below for the sponsor inspection are based on a draft Establishment Inspection Report (EIR) and e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

- a. **What was inspected:** This inspection evaluated compliance with sponsor responsibilities including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA form 1572s, and quality assurance (QA). A review of the Trial Master Files was conducted. Special attention was requested for the following Ukrainian sites that were chosen for inspection but could not be inspected: Dr. Bondarenko, Site 4207 for Protocol NETU-08-18 and Site 4205 for Protocol NETU-10-29; and Dr. Dudnichenko, Site 213 for Protocol NETU-07-07. In addition, coverage of Dr. Popov, Site 120 for Protocol NETU-07-07 was requested because the sponsor noted in the clinical study report that there were “multiple major audit findings, ranging from failure to meet eligibility criteria and administration of prohibited medications to inconsistencies between source data and CRFs.” These were noted after the study was closed.

The number of monitoring files reviewed by the FDA investigator, per study:

- NETU-07-07 – Site 210 (Dr. Popov), Site 213 (Dr. Dudnichenko) and 2 additional sites, Site 215 and Site 105 (paper files only for this trial)
 - NETU-08-18 – Dr. Bondarenko (electronic records)
 - NETU-10-29 - Dr. Bondarenko plus 3 others randomly chosen (electronic records)
 - PALO-10-01 - 2 randomly chosen sites reviewed in detail (electronic records)
- b. **General observations/commentary:** The sponsor delegated complete responsibility to a CRO for each of these four trials. The CRO selection process was found to be more robust currently and for the latter 3 studies than it was for the initial NETU-07-07 study (initiated in 2007). Concerning the conduct and oversight of NETU-07-07, the Phase II study was initiated in 2007, and was “upgraded” to a pivotal study to be included in the NDA after discussions with FDA in 2010. While the study was ongoing, issues that arose and were noted at Site 120 in Weekly Activities reports included items such as ECGs were not transmitting by phone in some areas, the timing of ECGs and vital signs, the drug supply had repeated issues related to temperatures during transport, and the analog scale in the NCR pages was problematic in that there was a shift of values between the white and pink NCR pages.

Due to the change in study classification (Phase 2 to Phase 3) and the intent to include it in the NDA submission, the sponsor conducted 13 additional QA audits post-study at 12 sites in 2011 in addition to the original 8 site audits conducted in 2008 and 2009. Site 120 underwent 2 post study audits for data verification and re-verification. At Site 120, the more critical issues revealed during the audits included 21 eligibility issues and the 27 subjects that were found to have unreported adverse events or concomitant medications. The eligibility issues were primarily medication related, i.e. having taken an antiemetic within 24 hours or taken dexamethasone within 4 weeks, but there were also 2 subjects who exhibited some exclusionary criteria in their ECG. Many notes were created by Dr. Popov to explain the issues, but many simply stated that the item was an oversight and not intentional. However, study data could not be added or changed because the database had already been locked by this time.

Financial disclosure documents were reviewed extensively and only minor checking or dating issues were found with a very small number of these.

- c. **Assessment of data integrity:** There was no evidence through the monitoring reports and QA audits performed to indicate non-compliant PIs (other than Site 120 for Study NETU 07-07) or any under-reporting of AEs. It appears that the issues noted at Site 120 for Study NETU 07-07 were an isolated occurrence and that, other than this instance, the Helsinn oversight of the CROs involved with the 4 studies appeared adequate. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Six clinical investigator sites and the sponsor were inspected for this NDA. Coverage of two clinical sites per protocol was achieved with the exception of NETU 07-07. All clinical sites had the classification of NAI or VAI with minor regulatory violations cited. For the sponsor inspection, inspection of monitoring reports provided insight into good clinical practice (GCP) issues noted by the sponsor at Site 120 for Study NETU 07-07. The draft inspection report noted that the issues with Site 120 for Study NETU 07-07 were isolated and related to the unique development plan for this FDC drug. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

Note: Observations above for the sponsor inspection are based on a draft EIR and e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Medical Reviewer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
05/13/2014

SUSAN D THOMPSON
05/14/2014

KASSA AYALEW
05/14/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 12, 2014

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Error Products
(DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Meeta Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): AKYNZEO (netupitant and palonosetron)

Dosage Form and Route: capsules

Application Type/Number: NDA 205-718

Applicant: Helsinn Healthcare SA

1 INTRODUCTION

On September 27, 2013, Helsinn Healthcare SA submitted for the Agency's review an original New Drug Application (NDA) 205-718 for AKYNZEO (netupitant and palonosetron) capsules. The proposed indications for AKYNZEO (netupitant and palonosetron) capsules are for:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.
- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) on October 10, 2013 and October 24, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for AKYNZEO (netupitant and palonosetron) capsules.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the proposed container label, carton labeling and Full Prescribing Information was completed on January 19, 2014.

2 MATERIAL REVIEWED

- Draft AKYNZEO (netupitant and palonosetron) PPI capsules received on September 27, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on April 25, 2014.
- Draft AKYNZEO (netupitant and palonosetron) capsules Prescribing Information (PI) received on September 27, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on April 25, 2014.
- Approved EMEND (aprepitant) capsules comparator labeling dated March 20, 2013.
- Draft ALOXI (palonosetron HCl) comparator labeling dated April 25, 2014.
- Draft AKYNZEO (netupitant and palonosetron) Instructions for Opening dated April 25, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB)

published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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NATHAN P CAULK
05/12/2014

MEETA N PATEL
05/13/2014

BARBARA A FULLER
05/13/2014

LASHAWN M GRIFFITHS
05/13/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: May 6, 2014

To: Mary Chung, Pharm D
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205718
OPDP Comments for draft Akynzeo (netupitant and palonosetron)
capsules for oral use PI and PPI

OPDP has reviewed the proposed draft PI for Akynzeo (netupitant and palonosetron) capsules for oral use. We have reviewed the draft PI, sent to us on April 25, 2014, and have the following comments. Comments on the draft PPI will be sent under separate cover as a joint review with DMPP.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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MEETA N PATEL
05/06/2014

STUDY ENDPOINT CONSULT REVIEW

Template version: November 8, 2013

SEALD TRACKING NUMBER	2013-174
IND/NDA/BLA NUMBER	NDA 205718
LETTER DATE/SUBMISSION NUMBER	09/25/2013
PDUFA GOAL DATE	09/26/2014
DATE OF CONSULT REQUEST	11/19/2013
REVIEW DIVISION	Division of Gastroenterology and Inborn Errors Products
MEDICAL REVIEWER	Nancy Snow/Ruyi He
REVIEW DIVISION PM	Mary Chung
SEALD REVIEWER(S)	Paivi Miskala
ACTING SEALD ENDPOINTS TEAM LEADER	Elektra Papadopoulos
ACTING SEALD DIRECTOR	Sandy Kweder
REVIEW COMPLETION DATE	04/24/2014
DRUG NAME	Akynzeo™ (netupitant and palonosetron) capsules, for oral use
SPONSOR/APPLICANT	Helsinn Healthcare
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
ENDPOINT(S) CONCEPT(S)	Nausea
MEASURE(S)	Average nausea visual analog scale
SPONSOR'S TARGETED INDICATION	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy

A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Gastroenterology and Inborn Errors Products (DGIEP) regarding NDA 205718 for Akynzeo™ (netupitant and palonosetron capsules, for oral use). Based on information provided by the sponsor, the sponsor is targeting an indication for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy. DGIEP consulted SEALD regarding the Functional Living Index-Emesis (FLIE) (see SEALD review signed off in Darrrts 03/04/2014). Following discussion of the FLIE instrument during a labeling meeting on March 12, 2014, DGIEP requested a second SEALD consult regarding sponsor's nausea assessment. Given the short turnaround for the second SEALD consult, this review was abbreviated to summarize the key issues.

Sponsor assessed average nausea severity in the past 24 hours using a 100mm visual analog scale where 0 indicates "no nausea" and 100 indicates "nausea as bad as it could be". This assessment is used as part of combination endpoints and as stand-alone endpoints in sponsor's trials. Regulatory history under IND 73493 suggests that there is documented agreement between DGIEP and the sponsor on some of the key trial endpoints in some of the trials. SEALD defers determination of key secondary endpoints (i.e., adequacy of multiplicity adjustment in the statistical analysis plan) to the statistical reviewer. Sponsor proposes to (b) (4) Key issues regarding the nausea assessment are as follows:

- a) Non-key endpoints which were not included in the multiplicity adjustment of the statistical analysis plan do not provide conclusive evidence of treatment benefit (b) (4)
- b) Sponsor's instrument measures average nausea severity, not worst nausea severity in the past 24 hours. This could be problematic since the sponsor is defining "no nausea" as maximum nausea severity < 5 mm as measured on the VAS and "no significant nausea" as maximum nausea severity < 25 mm (maximum refers to maximum average severity of nausea recorded within the time interval to be analyzed, i.e., within overall phase 0-120 hours, acute phase 0-24 hours, delayed phase 25-120 hours,). With average nausea measurement there is no guarantee that maximum average nausea severity was <5 mm in any given day because we are measuring an average, not the worst experience patient had with nausea. For example, it is possible that a patient had nausea > 5mm part of the day, but could have an average nausea measurement of <5 for the day. There is a similar issue with "no significant nausea" cutpoint of < 25 mm using average nausea measurement; it is possible that a patient had significant nausea at some point during the day, but could end up with an average < 25 mm for the day. This would be less problematic if the sponsor had measured worst nausea severity because we would have had some certainty that the nausea was never worse than the cutpoint values during the past 24 hours. Sponsor was requested a copy of the instrument and any empiric evidence to support

these cutpoints ; sponsor responded by sending a copy of the nausea instrument (see appendix of this review) and by referring to the previous labeling for EMEND, but did not provide any additional empiric evidence or justification to support the nausea cutpoints. Thus, there continues to be some uncertainty whether any claims regarding “no nausea” or “no significant nausea” would be misleading based on the prespecified cutpoints given the average nausea measurement. If the sponsor had used the score of 0 as a definition of “no nausea” then that would have been a more appropriate definition because if the average for the day is 0 then the maximum for the day would likely be 0 as well. DGIEP could consider further evaluation of the sponsor’s trial data to look at distribution of nausea scores for patients who had a nausea score < 5mm; what percentage of these patients in each treatment arm have a score of 0?

- c) Nausea endpoints cannot be interpreted without information on rescue medication use to ensure that any improvement in nausea is not due to rescue medication use (i.e., similarly to how pain endpoints are evaluated).
- d) In general, using a 100 mm visual analog scale is acceptable, but one should keep in mind that a visual analog scale may give a false sense of precision because it is questionable that patients can a) differentiate 101-levels in dyspnea severity and b) can visually accurately draw a line without error using these 101-levels, yet we are measuring the patient responses with a 100 mm ruler.
- e) Submission did not include information if any validation or translation/cultural adaptation work was done for the nausea assessment.

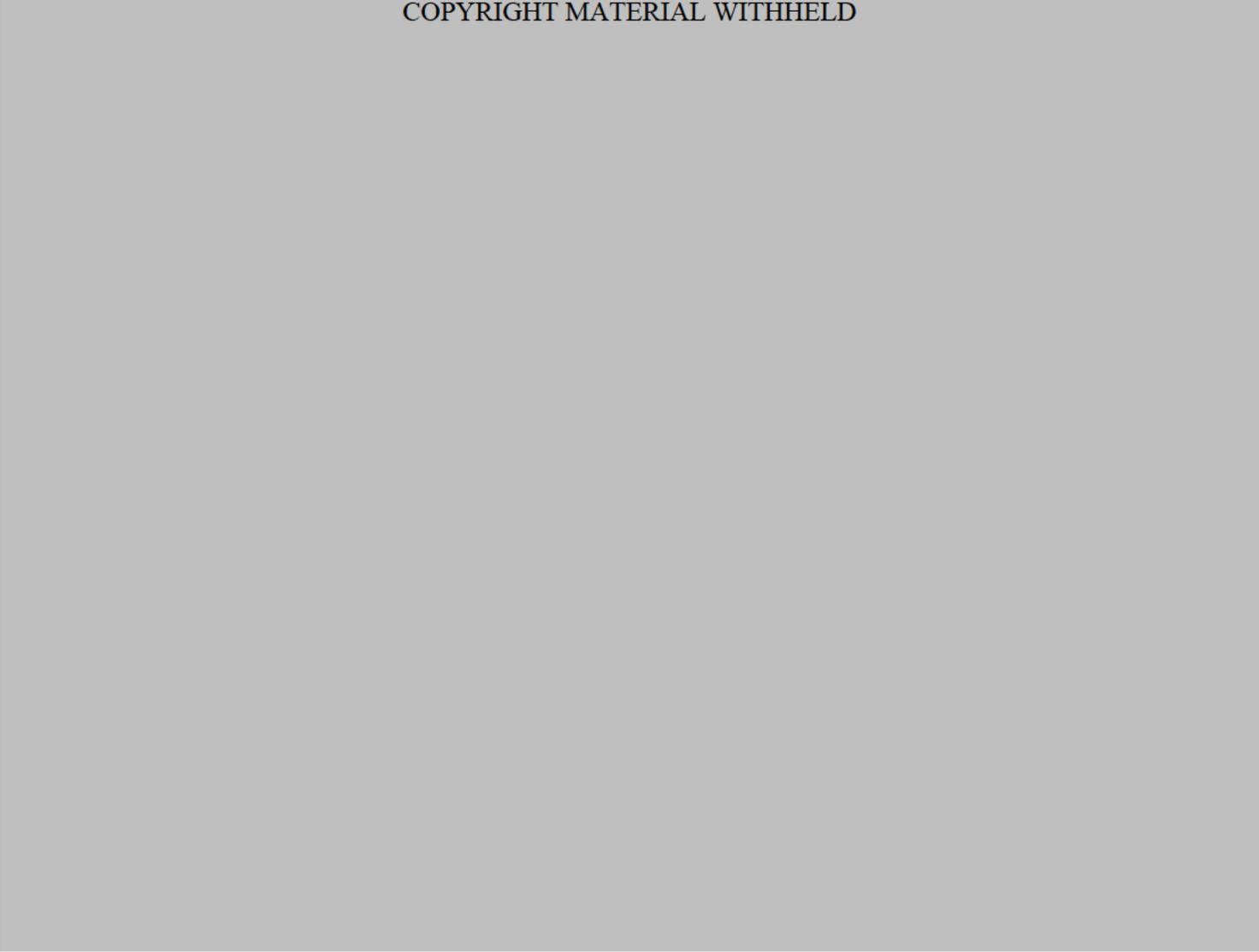
This review concludes that if any of the nausea endpoints were key endpoints in a phase 3 trial and there is a prior agreement with the FDA on key endpoints then SEALD recommends conservative evaluation of those endpoints to support treatment benefit claims, given the limitations above, to ensure that there is convincing evidence of treatment benefit. The sponsor is adequately measuring average nausea severity based on the instrument, although this was not ideal in this particular context. The most challenging limitation is lack of evidence to support the cutpoints chosen for “no nausea” and “no significant nausea” given the average nausea measurement. Also, rescue medication use must be considered when evaluating nausea. (b) (4)

[REDACTED]

SEALD defers evaluation of the effect of handling of missing values to DGIEP and Office of Biometrics. SEALD defers evaluation of treatment efficacy to DGIEP and Office of Biometrics.

B. APPENDICES

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ELEKTRA J PAPADOPOULOS
04/24/2014

STUDY ENDPOINT CONSULT REVIEW

Template version: November 8, 2013

SEALD TRACKING NUMBER	2013-174
IND/NDA/BLA NUMBER	NDA 205718
LETTER DATE/SUBMISSION NUMBER	09/25/2013
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SEALD REVIEWER(S)	Paivi Miskala
ACTING SEALD ENDPOINTS TEAM LEADER	Elektra Papadopoulos
ACTING SEALD DIRECTOR	Sandy Kweder
REVIEW COMPLETION DATE	03/04/2014
DRUG NAME	Akynzeo™ (netupitant and palonosetron) capsules, for oral use
SPONSOR/APPLICANT	Helsinn Healthcare
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
ENDPOINT(S) CONCEPT(S)	Impact of nausea and vomiting on daily life
MEASURE(S)	Functional living index – emesis (FLIE)
INDICATION	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy

A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Gastroenterology and Inborn Errors Products (DGIEP) regarding NDA 205718. The sponsor has investigated efficacy and safety of oral netupitant administered in combination with palonosetron and dexamethasone compared to oral palonosetron and dexamethasone for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy. DGIEP is consulting SEALD regarding sponsor's proposal to include claims related to [REDACTED] (b) (4). [REDACTED] FLIE was not a key trial endpoint in the sponsor's phase 3 trials.

The consult concludes that [REDACTED] (b) (4). [REDACTED] Non-key endpoints, including FLIE, will be considered exploratory evidence, [REDACTED] (b) (4). Furthermore, the sponsor did not submit any information to support development and validation (i.e., content validity, psychometric validation, translation and cultural adaption) of the FLIE. At face value it is questionable whether patients can determine independent contributions of nausea and vomiting on their daily life when both of these symptoms are present (see section 3 for additional review findings regarding FLIE item content). For these reasons SEALD will not be requesting additional information from the sponsor (SEALD does not review development and validation of exploratory endpoints) unless DGIEP is considering [REDACTED] (b) (4). [REDACTED]

B. COMMENTS TO SPONSOR/APPLICANT

Not applicable.

C. STUDY ENDPOINT REVIEW

*** Information related to FLIE was collected in one of the sponsor's two phase 3 trials (NETU-08-18 included FLIE, NETU-10-29 did not include FLIE). For that reason the remainder of this review will focus on NETU-08-18. ***

1 CONTEXT OF USE (COU)

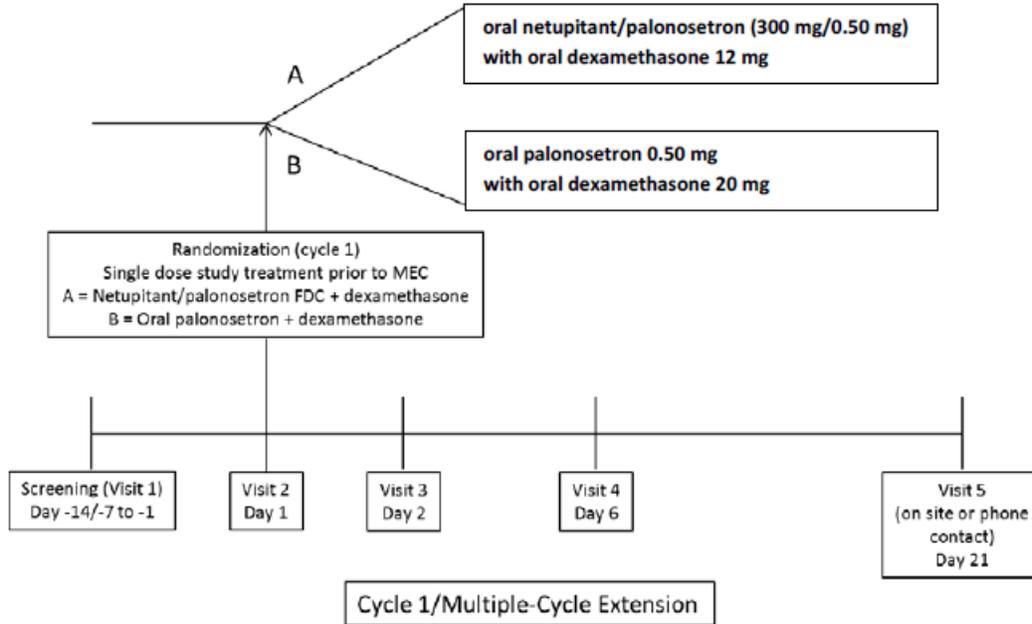
1.1 Target Study Population and Clinical Setting

Cancer patients receiving moderately emetogenic chemotherapy.

1.2 Clinical Trial Design

NETU-08-18 was a phase III multicenter/multinational (177 study sites in 15 countries), randomized, double-blind, double-dummy, active-controlled, parallel group study stratified (by region (United States, Latin America including Mexico, Europe, Commonwealth of Independent States (i.e, former Soviet Republics) and Asia) and age (<55 years and \geq 55 years). The study was designed to evaluate the efficacy and safety of oral netupitant administered in combination with palonosetron and dexamethasone compared to oral palonosetron and dexamethasone for the prevention of nausea and vomiting in cancer patients receiving moderately emetogenic chemotherapy.

Sponsor included the following diagram outlining NETU-08-18 clinical trial design:



Abbreviations: FDC=Fixed-Dose Combination; MEC=Moderately Emetogenic Chemotherapy.

Figure 1: Study Design and Plan

1.3 Endpoint Positioning

Sponsor outlined the following endpoints in their NETU-08-18 phase 3 trial:

SEALD Review

Paivi H. Miskala, PhD

NDA 205718

Efficacy: The primary efficacy endpoint was the proportion of patients with CR (defined as no emesis, no rescue medication) in the delayed phase (time interval 25-120 hours after the start of the MEC administration) at cycle 1.

Key secondary efficacy endpoints were defined at cycle 1 as the proportion of patients with:

- CR during the acute phase (0-24 hours).
- CR during the overall phase (0-120 hours).

Other secondary efficacy endpoints were defined at cycle 1 as the proportion of patients with:

- No emesis during the delayed, acute, and overall phase.
- No rescue medication during the delayed, acute, and overall phase.
- No significant nausea (Visual Analogue Scale [VAS] <25 mm) during the delayed, acute, and overall phase.
- No nausea (VAS <5 mm) during the delayed, acute, and overall phase.
- Complete protection (no emesis, no rescue medication and no significant nausea [maximum nausea VAS <25 mm]) during the delayed, acute, and overall phase.
- Total control (no emesis, no rescue medication and no nausea [maximum VAS <5 mm]) during the delayed, acute, and overall phase.

Other efficacy endpoints at cycle 1 were defined as follows:

- Severity of nausea, defined as the maximum nausea on the VAS in the acute, delayed, and overall phase.
- Time to first emetic episode, time to first rescue medication intake, and time to treatment failure (based on time to the first emetic episode or time to the first rescue medication intake, whichever occurs first).
- Impact on patients' daily life activities for the first 120 hours following the administration of MEC as assessed by the Functional Living Index-Emesis (FLIE) questionnaire.

Secondary efficacy endpoints evaluated during the multiple-cycle extension were the proportion of patients with:

- CR during the delayed, acute, and overall phase following subsequent cycles of MEC.
- No significant nausea during the delayed, acute, and overall phase following subsequent MEC cycles.

Reviewer's comments: FLIE instrument was not specified as a key study endpoint. Non-key endpoints will be considered exploratory in nature.

(b) (4)

NETU-08-18

Table 3: Study Visits and Assessments

	Cycle 1/Multiple-Cycle Extension				
	Screening Day -14/-7 to -1	Day 1	Day 2 ^a	Day 6 ^b	Day 21 ^c
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Informed consent	(X) ^d				
Inclusion/exclusion criteria	X	X			
Demography	(X) ^d				
Medical history	(X) ^d				
ECOG performance status	X				
Urine pregnancy test	X	(X) ^k			
Prior and concomitant medications	X	X	X	X	X
Physical examination	X		X	X	
Vital signs ^e	X	X	X	X	
12-lead ECG ^f	X ^g	X ^g	X ^g	X ^g	
LVEF	(X) ^d				(X) ^h
Cardiac troponin	(X) ^d		X ^a	X	
Blood chemistry	X		X	X	
Hematology	X		X	X	
Urinalysis	X		X	X	
Randomization		(X) ^d			
Chemotherapy		X			
Study drugs and additional study drug administration		X			
Patient diary and instructions on completion		Completed from Day 1 to Day 5, collected at Visit 4			
FLIE questionnaire				(X) ^d	
Adverse events	X	X	X	X	X
Pharmacokinetics		(X) ^d	(X) ^d	(X) ^d	

- a Approximately 24 hours after the first study drug administration on Day 1.
b 120 hours after the first study drug administration on Day 1. If Day 6 was a holiday or a weekend day Visit 4 was to be scheduled within the 2 forthcoming days.
c Day 21±2, either on-site or phone contact. If following chemotherapy cycle was scheduled 21 day after Day 1 of previous cycle, the follow-up visit and the screening visit of 2 consequent cycles may have coincided.
d Only at cycle 1.
e Vital signs included pulse rate, systolic blood pressure, and diastolic blood pressure at Visit 1, pre-dose, 5 hours, 24 hours, and 120 hours after the first study drug administration on Day 1 of each cycle; height was measured only at Visit 1 of cycle 1, weight at Visit 1 and Visit 4 of each cycle.
f 12-lead ECG (single recording) was assessed in a central laboratory.
g 12-lead ECG was recorded at screening, pre-dose, 5 hours, 24 hours, and 120 hours after the first study drug administration on Day 1 of each cycle.
h End of study only.
i Adverse events were collected from Informed Consent to 21 days after Day 1 of last cycle.
j During cycle 1, in a subgroup of patients, blood samples at pre-specified time schedules for PK.
k Performed for females of childbearing potential within 24 hours prior to the first study drug administration on Day 1 of each cycle.

Abbreviations: ECG=Electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FLIE=Functional Living Index-Emesis; LVEF=Left Ventricular Ejection Fraction; PK=Pharmacokinetics.

1.4 Labeling or promotional claim(s) based on the COA

Sponsor is proposing the following draft labeling language regarding (b) (4)



Reviewer's comments: (b) (4)

Furthermore, the sponsor submission did not include any information related to development and validation of this instrument to determine whether the instrument measures what it is intended to measure. At face value the instrument is problematic; see section 3 below.

2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

Conceptual framework was not included in the submission. Sponsor states that the instrument measures the impact of nausea and vomiting on daily life. See section 3 below for the content of the instrument domains.

3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

Functional Living Index-Emesis (FLIE)

Sponsor states that the FLIE measures the impact of nausea and vomiting on patients' quality of life.

FLIE has 18 questions divided into 2 domains:

a) Nausea (questions 1-9):

Q1: How much nausea have you had in the past 5 days?

SEALD Review

Paivi H. Miskala, PhD

NDA 205718

Q2: Has nausea affected your ability to maintain usual recreation or leisure activities in the past 5 days?

Q3: Has nausea affected your ability to make a meal or do minor household repairs during the past 5 days?

Q4: How much has nausea affected your ability to enjoy a meal in the past 5 days?

Q5: How much has nausea affected your ability to enjoy drinking liquids in the past 5 days?

Q6: How much has nausea affected your willingness to see and spend time with family and friends, in the past 5 days?

Q7: Has nausea affected your daily functioning in the past 5 days?

Q8: Rate the degree to which your nausea has imposed a hardship on you (personally) in the past 5 days?

Q9: Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 5 days?

b) Vomiting (questions 10-18):

Q10: How much vomiting have you had in the past 5 days?

Q11: Has vomiting affected your ability to maintain usual recreation or leisure activities during the past 5 days?

Q12: Has vomiting affected your ability to make a meal or do minor household repairs during the past 5 days?

Q13: How much has vomiting affected your ability to enjoy a meal in the past 5 days?

Q14: How much has vomiting affected your ability to enjoy drinking liquids in the past 5 days?

Q15: How much has vomiting affected your willingness to see and spend time with family and friends, in the past 5 days?

Q16: Has vomiting affected your daily functioning in the past 5 days?

Q17: Rate the degree to which your vomiting has imposed a hardship on you (personally) in the past 5 days?

Q18: Rate the degree to which your vomiting has imposed a hardship on those closest to you in the past 5 days?

Sponsor states that each question is answered using a 100mm (1-7 points) visual analogue scale with anchors corresponding to “none”/“not at all” and “a great deal”.

Sponsor outlines in their submission that the instrument is scored as follows:

- for questions 1, 2, 4, 5, 7, 8, 9, 10, 12, 13, 14, 16, and 17:

subtract the distance in mm from 100 (Score=100-distance).

- for questions 3, 6, 11, 15, and 18 (for which scale anchors are in the opposite direction compared to the other questions):

the distance in mm is the score for the question (Score=distance).

The minimum score for any question is 0 mm and the maximum score is 100 mm.

Sponsor provided the following formula for calculation of the nausea and vomiting domain scores:

$$\text{Domain score (in mm)} = \frac{\sum \text{item scores (in mm)}}{\text{no. items answered}} \times 9$$

$$\text{Domain score (in FLIE points)} = (\text{Domain score in mm} \times 0.06) + 9$$

Instrument domain scores range from 9 to 63.

FLIE total score is the sum of the nausea and vomiting domain scores.

The instrument uses 5-day recall period.

Reviewer's comments: At face value this instrument is problematic for the following reasons:

- *It is questionable whether patients can determine independent contributions of nausea and vomiting on their functioning in daily life if both of these symptoms occur.*
- *The domain scores combine symptom severity (Q1, Q10) with impact of having each symptom to their daily life; therefore, the measurement concept is unclear.*
- *Q9 and Q18 ask about hardship to others which is not a relevant concept to measure when evaluating treatment benefit to the person himself/herself.*
- *Rationale for creating "FLIE points" scores is unclear.*

Sponsor did not provide a copy of the instrument in their submission. The case report form that was included in the submission did not show the visual analog scales as presented to the patient. No evidence to support instrument development and validation (i.e., content validity, psychometric validation, and translation and cultural adaptation evidence) was included in the submission.

4 CONTENT VALIDITY

Content validity information was not included in the submission. Also, SEALD does not review development and validation of exploratory endpoints.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

Information related to other measurement properties was not included in the submission.

6 INTERPRETATION OF SCORES

Information was not included in the submission.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

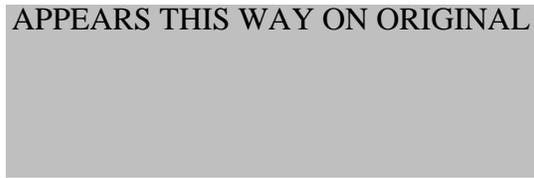
Information was not included in the submission.

8 REVIEW USER MANUAL

User manual was not included in the submission.

D. APPENDICES

APPEARS THIS WAY ON ORIGINAL



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/s/

PAIVI H MISKALA
03/04/2014

ELEKTRA J PAPADOPOULOS
03/04/2014



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 3, 2014

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Mary Chung, RPM
DGEIP

Subject: QT-IRT Consult to NDA 205718

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated Nov 20, 2013 regarding the sponsor's response to our previous request for ECG data at 15 and 30 minutes. The QT-IRT received and reviewed the following materials:

- Your consult
- IRT previous review (1/20/2010)
- Draft Label

QT-IRT Comments for DGEIP

The sponsor's response to the QT-IRT's previous request is acceptable.

PROPOSED LABEL

SPONSOR'S PROPOSED LABEL

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

QT-IRT'S PROPOSED LABEL

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

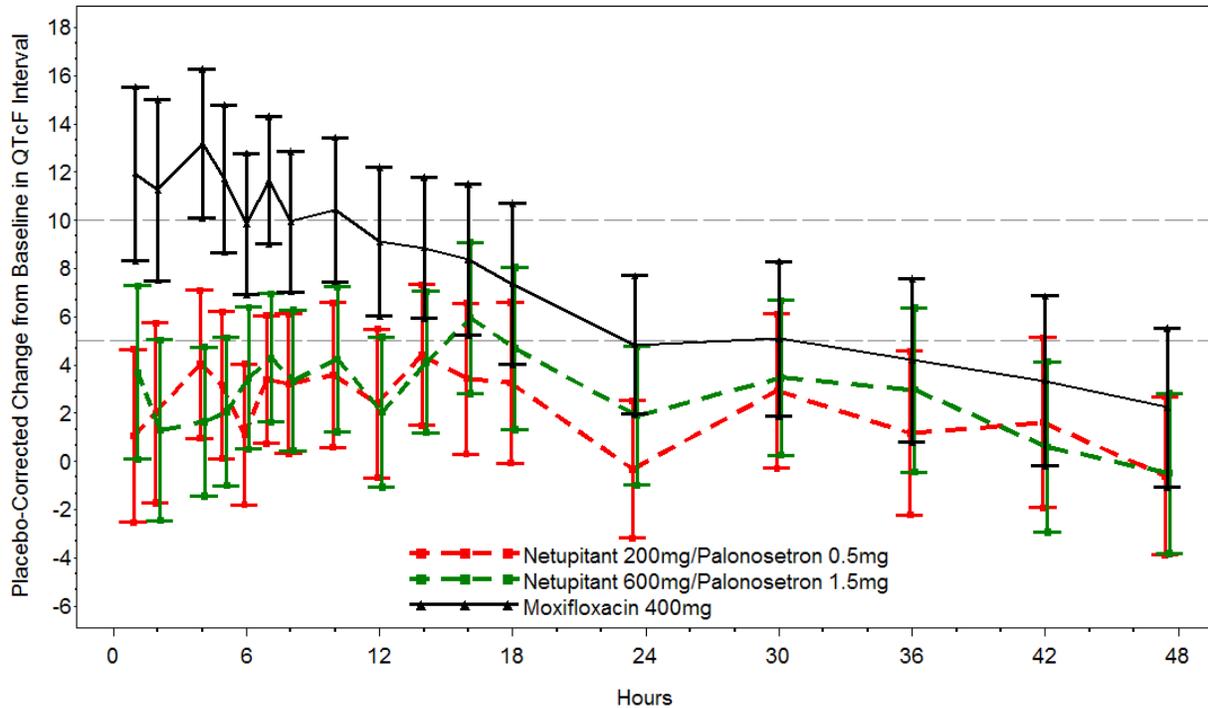
(b) (4)

BACKGROUND

We have previously reviewed the QT study report for this application when it was submitted under IND 73493. In our review we stated that "No significant QTcF prolongation effect of netupitant/palonosetron (therapeutic dose 200 mg/0.50 mg and suprathapeutic dose 600 mg/1.50 mg) was detected in this TQT study (Figure 1)." However, we made the following comment to be conveyed to the sponsor:

"The moxifloxacin profile is not exactly what we expected. The rising phase is missing. The maximum moxifloxacin induced ddQTcF effect appears almost at the first available time point, which is 1 hr after dose. We want to understand what happened before hour 1. Please extract data for moxifloxacin, placebo at 15b minute, 30 minute post-dose and the corresponding baseline for us to evaluate."

Figure 1: LS Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



Note: CIs are all unadjusted including moxifloxacin.

Source: IRT previous review (1/20/2010), Page 24.

The sponsor responded to the above request during the current NDA submission as the following:

Due to the timing of the start and end of the 24 hour recordings, there were no data at the Day-1 equivalent of 15 and 30 minutes post dose, since the ECG Holter recording start time was not done on Day -1 with respect to the time of dosing on Day 1. Thus, extractions could only be taken at 35 minutes and 45 minutes post dose on Day 1 of moxifloxacin dosing that corresponded to the equivalent times on Day -1. These data show that there was an increase in QTc at 35 minutes and at 45 minutes similar to the 1 hour time point; hence not showing the expected rise in the moxifloxacin result profile (see Table below).

Placebo-Corrected Change from Baseline - Estimates from Mixed Model ANOVA [1]
 QTc Fridericia (msec)
 Additional Exploratory Analysis to Investigate Early Moxifloxacin QTc Effects

Moxifloxacin 400 mg			
Time	Estimate [1]	Upper Bound [2]	Lower Bound [2]
35 min	12.5	15.5	9.4
45 min	12.6	15.6	9.6
1 hr	11.3	14.3	8.3
2 hr	10.5	13.6	7.5
4 hr	12.9	15.9	9.9
5 hr	11.4	14.4	8.4
6 hr	9.5	12.5	6.5

Moxifloxacin can show an increase in QTc duration after 30 minutes from dosing and the critical time point to determine rise is the 15 minute time point which due to study condition from several years ago was not recorded. While assay sensitivity is shown statistically the clinical profile of moxifloxacin from 0-60 minutes could not be ascertained. Since the pharmacodynamic-kinetic model showed absolutely no hint of any effect of the study agents on cardiac repolarization the integrity of the results of the trial should not be seriously questioned.

Since however the ECG data and the pharmacokinetic-dynamic modelling were completely void of any signal of an effect on cardiac repolarization for this trial, the integrity of the results should not be seriously questioned.

Reviewer's comments: Acceptable. The relationships between $\Delta\Delta QTcF$ and drug concentrations were independently investigated in our previous review and no evident exposure-response relationships were observed.

Thank you for requesting our input into the development of this product under NDA 205718. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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/s/

JIANG LIU
03/03/2014

NORMAN L STOCKBRIDGE
03/03/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: January 17, 2014

Reviewer: Terri Wood-Cummings, MD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, M.S., Pharm.D
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Akynzeo (Netupitant and Palonosetron) Capsules
300 mg/0.5 mg

Application Type/Number: NDA 205718

Applicant/sponsor: Helsinn Healthcare SA

OSE RCM #: 2013-2266

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	INTRODUCTION.....	1
1.1	Regulatory History.....	1
1.2	Product Information.....	1
2	METHODS AND MATERIALS REVIEWED.....	1
2.1	Previously Completed Reviews.....	2
2.2	Labels and Labeling.....	1
3	MEDICATION ERROR RISK ASSESSMENT.....	2
4	CONCLUSIONS.....	2
4	RECOMMENDATIONS AND COMMENTS.....	2
	Appendices.....	4

1 INTRODUCTION

This review responds to a consult from the Division of Gastroenterology and Inborn Errors Products (DGIEP) to evaluate the proposed container label, carton labeling, and Full Prescribing Information for Akynzeo (NDA 205718) for areas of vulnerability that could lead to medication errors.

DGIEP requested this review as part of their evaluation for NDA 205718.

1.1 PRODUCT INFORMATION

The following product information is provided in the Applicant's September 27, 2013 submission:

- Active Ingredients: Netupitant and Palonosetron
- Indication of Use: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy; prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Route of Administration: Oral
- Dosage Form: Capsules
- Strength: 300 mg/0.5 mg
- Dose and Frequency: One capsule orally one hour prior to the start of chemotherapy.
- How Supplied: Blister pack of one capsule.
- Storage: Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59° - 86°F).
- Container and Closure System: Product is supplied in an (b) (4) foil blister pack, one capsule per blister pack card. The blister card is packaged in secondary, (b) (4) (Burgopak) packaging.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted September 27, 2013 (Appendix A)
- Carton Labeling submitted September 27, 2013 (Appendix B)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Instructions for Opening Diagram submitted September 27, 2013 (Appendix C)
- Full Prescribing Information submitted September 27, 2013

3 MEDICATION ERROR RISK ASSESSMENT

The Applicant is proposing a combination product that contains Netupitant and Palonosetron. Although Palonosetron is currently marketed, Netupitant is a new molecular entity, and this is the first combination product containing these two ingredients. The product is supplied in an (b) (4) foil blister pack containing one capsule and packaged in a secondary, (b) (4) Burgopak. This packaging configuration is supported by the dosage and administration for this product which is one capsule prior to chemotherapy.

We performed a risk assessment of the proposed Full Prescribing Information to identify deficiencies that may lead to medication errors. Additionally, we reviewed the proposed container label and carton labeling to identify areas of improvement. We note that the dosage form is missing and the established name and strength are blended together making each more difficult to differentiate. We provide label and labeling recommendations in Section 5 to increase prominence of important information to ensure safe use of the product.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label and to promote the safe use of the product.

5 RECOMMENDATIONS AND COMMENTS

DMEPA recommends the following be implemented prior to approval of this NDA:

5.1 COMMENTS TO THE APPLICANT

1. Burgopak Label and Carton Labeling

- a. As currently presented, the dosage form is not present. The established name presentation should include the active ingredient followed by the dosage form. Include the dosage form “capsules” on all labels and labeling immediately following the active ingredient presentation. Ensure the dosage form presentations is commensurate with the prominence of the active ingredient presentation.
- b. As currently presented, the established name presentation uses a (b) (4) font against a white background which makes it difficult to read. Revise the font color to increase the prominence of the established name so that it is commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10 (g)(2).
- c. The components of the established name and strength “*netupitant 300 mg, palonosetron 0.5 mg*” appear blended together making each more difficult to differentiate. Revise the presentations of the established name and

strength so that the established name appears on one line directly beneath the proprietary name and the strength appears on one line directly beneath the established name to increase legibility and differentiation of each, e.g.,

“Alynzeo”

“(netupitant and palonosetron) capsules”

“300 mg and 0.5 mg”

- d. The ^{(b) (4)} located to the left of the proprietary name is prominent and may be misinterpreted as part of the proprietary name. Delete this ^{(b) (4)} or ^{(b) (4)} and relocate away from the proprietary name.

2. Instructions for Opening Diagram

The written instructions for opening the BurgoPak on the container label and in the Instructions for Opening Diagram are adequate. However, we recommend revising the pictures accompanying the first two steps, “1. Press buttons A & B together,” and “2. Pull tab with other hand,” to depict the hand holding the Burgopak grasping the Burgopak from the rear rather than ^{(b) (4)} where the blister pack emerges.

If you have further questions or need clarifications, please contact Mary Chung, Project Manager, at 301-796-0260.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TERRI WOOD-CUMMINGS
01/17/2014

LUBNA A MERCHANT
01/19/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205718	NDA Supplement #: Not applicable (N/A)	Efficacy Supplement Type SE- N/A
Proprietary Name: AKYNZEO Established/Proper Name: netupitant/palonosetron Dosage Form: fixed-dose combination capsule Strengths: 300 mg netupitant/ 0.5 mg palonosetron		
Applicant: Helsinn Healthcare Agent for Applicant (if applicable): August Consulting		
Date of Application: 9/27/2013 Date of Receipt: 9/27/2013 Date clock started after UN: N/A		
PDUFA Goal Date: 9/26/2014	Action Goal Date (if different): N/A	
Filing Date: 11/26/2013	Date of Filing Meeting: 10/25/2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy and moderately emetogenic cancer chemotherapy in adults (acute and delayed CINV HEC and MEC).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: PDUFA V	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 73493				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X	<input type="checkbox"/>		

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>	X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>	X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>	X	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>	X	
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug		<input type="checkbox"/>	X		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>) If yes , # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?	<input type="checkbox"/>	X	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) X All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	X	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X	<input type="checkbox"/>		The sponsor proposed to utilize NETU-07-07, a phase 2 study to demonstrate the efficacy of the netupitant component of the drug product. The agreement with FDA to utilize this trial as one of the four pivotal clinical trials to support this NDA was made after the completion of the
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				

				phase 2 study. As such, the collection of Financial Disclosure Forms was obtained retroactively because as a phase 2 study, Financial Disclosure Forms were not required upon initiation of the study. Completed and signed financial disclosure forms were obtained for 181 investigators out of a total of 196 investigators. The sponsor has shown due diligence in obtaining this information to fulfill their financial disclosure requirement for NETU-07-07.
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?	<input type="checkbox"/>	<input type="checkbox"/>	X	

<i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>				
<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff: 10/8/13</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff: N/A</i></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u>	X	<input type="checkbox"/>		
<p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?	<input type="checkbox"/>	<input type="checkbox"/>	X	
<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter</i>				
<u>BPCA</u> (NDAs/NDA efficacy supplements only):	<input type="checkbox"/>	X		
Is this submission a complete response to a pediatric Written Request?				
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	X	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card			

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: QT Interdisciplinary Review Team: 11/15/2014 SEALD: 11/18/2014</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): July 20, 2009 <i>If yes, distribute minutes before filing meeting</i>	X	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 16, 2013 <i>If yes, distribute minutes before filing meeting</i>	X	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): January 22, 2010 and July 15, 2010 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X	<input type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/25/2013

BLA/NDA/Supp #: NDA 205718

PROPRIETARY NAME: AKYNZEO

ESTABLISHED/PROPER NAME: netupitant/palonosetron

DOSAGE FORM/STRENGTH: fixed-dose combination capsule

APPLICANT: Helsinn Healthcare

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

1. Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (CINV HEC)
2. Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV MEC)

BACKGROUND: On September 15, 2006, Helsinn Healthcare submitted IND 73493 netupitant palonosetron fixed-dose combination capsule for treatment of chemotherapy induced nausea and vomiting. Helsinn's clinical development program was discussed at the end-of-phase 2 meeting held on July 20, 2009. A series of Special protocol Assessment (SPA) requests were submitted by the sponsor and Type A SPA meetings were held January 22, 2010 and July 15, 2010. Per discussion from these meetings, four clinical studies (NETU-07-07, PALO-10-01, NETU-08-18, and NETU-10-29) were conducted to support the efficacy and safety of the fixed-dose combination capsule for the prevention of acute and delayed phases of CINV-HEC and CINV-MEC. On April 16, 2013, a pre-NDA meeting was held to discuss the results of the phase 3 trials, the content and format of the planned eCTD NDA submission, proposed labeling and the schedule to submit the pediatric study plan.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mary Chung	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Ruyi He		Y
Clinical	Reviewer:	Nancy Snow	Y

	TL:	Ruyi He	Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Insook Kim	N
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Lisa Kammerman	N
	TL:	Freda Cooner	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ke Zhang	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Raymond Frankewich	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	Raymond Frankewich	Y
	TL:	Marie Kowblansky	Y
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	Lisa Khosla	Y
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	Yasmin Choudhry	N
	TL:	Kendra Worthy	N

OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	Y
	TL:	Susan Leibenhaut	Y
Controlled Substance Staff (CSS)	Reviewer:	Katherine Bonson	Y
	TL:	Silvia Calderon	N
Other reviewers	<ul style="list-style-type: none"> • Biopharmaceutics: Assadollah Noory, Banu Zonik, Tapash Ghosh (TL) • Pharmacometrics: Jingyu (Jerry) Yu • OSE/DPV: Christian Cao • OMP/PLT: Barbara Fuller • PMHS: Erica Radden 		
Other attendees	<ul style="list-style-type: none"> • ODE III: Julie Beitz (Director), Maria Walsh (ADRA), Giuseppe Randazzo (Regulatory Scientist) • DGIEP: Donna Griebel (Director), Andrew Mulberg (Deputy director) • OSE RPM: Phong (Pete) Do • ONDQA RPM: Rebecca McKnight 		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? 	<p>X YES</p> <p><input type="checkbox"/> NO</p>

If no , explain:	
<ul style="list-style-type: none"> Electronic Submission comments List comments:	X Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no , explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: Netupitant is an NME but not the first in its class. The application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease. The clinical study design was acceptable and the application did not raise significant safety or efficacy issues.
<ul style="list-style-type: none"> Abuse Liability/Potential Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CLINICAL MICROBIOLOGY	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES X NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	X YES <input type="checkbox"/> NO
If no , was a complete EA submitted?	X YES <input type="checkbox"/> NO
If EA submitted , consulted to EA officer (OPS)?	X YES <input type="checkbox"/> NO
Comments:	

<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES X NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	<p>N/A</p>

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Julie Beitz, Director, ODE III</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): February 12, 2014</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
X	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MARY H CHUNG
11/26/2013