CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205718Orig1s000

OFFICE DIRECTOR MEMO

MEMORANDUM

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

DATE: September 29, 2014

FROM: Julie Beitz, MD

SUBJECT: Approval Action

TO: NDA 205718 Akynzeo (netupitant and palonosetron) capsules
Helsinn Healthcare SA

Summary

Akynzeo is a fixed combination of netupitant, a selective antagonist of human substance P/neurokinin 1 (NK_1) receptors, and palonosetron, a 5-HT_3 receptor antagonist indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy (HEC). The palonosetron component of Akynzeo prevents acute nausea and vomiting, i.e., during the first 24 hours after the start of cancer chemotherapy. The netupitant component of Akynzeo prevents nausea and vomiting during both the acute and delayed phases of emesis, i.e., 0-120 hours after the start of chemotherapy.

Chemotherapeutic agents produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex. The development of acute emesis is known to depend on serotonin activation of 5-HT_3 receptors.[1] Palonosetron is a potent 5-HT_3 receptor antagonist, developed by Helsinn Healthcare SA. In 2003, an intravenous formulation was approved for adults at a dose of 0.25 mg for the prevention of 1) acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and 2) delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). In 2008, an oral formulation was approved for adults at a dose of 0.5 mg for the prevention of acute nausea and vomiting associated with initial and repeat courses of MEC. The manufacturer subsequently discontinued marketing of the oral formulation; FDA determined that marketing was not discontinued for reasons of safety or efficacy.

Delayed emesis[2] has been largely associated with the activation of tachykinin family NK_1 receptors in the central and peripheral nervous systems by substance P. As shown in *in vitro* and *in vivo* studies, netupitant, a new molecular entity, inhibits substance P mediated emesis.

This memo documents my concurrence with the Division of Gastroenterology and Inborn Errors Product's recommendation for approval of NDA 205718 for Akynzeo (netupitant and palonosetron) capsules in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Discussions regarding product labeling, and postmarketing study requirements and commitments have been satisfactorily completed. There are no inspectional issues that preclude approval.

Dosing

[1] Acute emesis refers to nausea and vomiting occurring 0-24 hours after the start of chemotherapy.
[2] Delayed emesis refers to nausea and vomiting occurring 25-120 hours after the start of chemotherapy.

A single Akynzeo capsule (300 mg netupitant/0.5 mg palonosetron) is administered approximately 1 hour prior to the start of chemotherapy; dexamethasone 12 mg is given orally 30 minutes prior to chemotherapy. Patients receiving highly emetogenic chemotherapy, including cisplatin-based chemotherapy, should also receive dexamethasone 8 mg orally on days 2 to 4. Dexamethasone administration on days 2 to 4 is not necessary for patients receiving anthracycline and cyclophosphamide based chemotherapy or chemotherapy not considered highly emetogenic. Akynzeo can be taken with or without food.

Regulatory History

Helsinn Healthcare SA submitted IND 073493 on September 14, 2006 (received on September 15, 2006) for a fixed combination of netupitant and palonosetron for the prevention of chemotherapy-induced nausea and vomiting. Helsinn proposed to develop the combination for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC).

On October 13, 2006, the sponsor requested that the IND be placed on inactive status. On July 20, 2009, an End-of-Phase 2 meeting was held to discuss completed and proposed controlled trials to support the indications sought. In correspondence dated August 7, 2009, received on August 10, 2009, the sponsor notified the Division of its intent to reactivate this IND.

Two phase 3 protocols were submitted for special protocol assessment in October 2009. One of these protocols was for Study (b) (4)

(b) (4)

The second protocol submitted for special protocol assessment was for Study NETU-08-18, designed to demonstrate the superiority of the 300 mg netupitant/0.5 mg palonosetron fixed combination vs. (b) (4) (b) (4) palonosetron in the proportion of patients receiving MEC who experienced a CR during the overall phase (i.e., 0-120 hours after the start of chemotherapy). In its response dated November 27, 2009, the Division recommended that the control arm be changed to oral 0.5 mg palonosetron to isolate the treatment effect of netupitant. If successful, the labeled indication would state that the contribution of the palonosetron component to the fixed combination is, in fact, what it is indicated for, namely, prevention of nausea and vomiting in the acute phase (0-24 hours) in patients with MEC.

In comments provided for both trials, the Division also recommended that cardiac troponin levels be drawn after netupitant dosing, based on cardiac toxicity seen with another NK_1 receptor antagonist.

A Type A meeting was requested and held on January 22, 2010 to discuss the Division's responses. Helsinn proposed to conduct a third controlled trial, Study PALO-10-XX, a non-inferiority trial comparing oral 0.5 mg palonosetron to IV 0.25 mg palonosetron in patients receiving HEC. Complete response in the acute phase of emesis (0-24 hours) was proposed as the primary endpoint. If successful, this trial would

establish the contribution of the oral palonosetron component in the combination product for HEC. The Division indicated that this additional trial may be an acceptable alternative to a third arm in Study (b) (4) (b) (4) in order to establish the contribution of oral palonosetron to the combination. Helsinn also proposed to utilize the completed phase 2 trial, Study NETU-07-07, to demonstrate the contribution of the netupitant component to the treatment effect of the combination in patients receiving HEC. Study NETU-07-07 was designed to assess the superiority of three single oral doses of netupitant (100 mg, 200 mg, and 300 mg) each combined with oral 0.5 mg oral palonosetron versus oral 0.5 mg palonosetron in patients receiving HEC.

On March 8, 2010, the Division issued written advice to Helsinn following an internal meeting with CDER's Office of Medical Policy. The Division stated that Study PALO-10-XX and Study NETU-07-07 taken together could support the proposed indication for the prevention of acute and delayed nausea and vomiting in patients receiving HEC. Furthermore, Study (b) (4) did not appear to be necessary. The Division also stated that for Study NETU-08-18 to support the proposed MEC indication, the protocol should be revised to include an active comparator arm of oral 0.5 mg palonosetron either as a third arm or as a replacement for the proposed (b) (4)

In March 2010, Helsinn submitted a revised protocol for Study NETU-08-18 for special protocol assessment. The proposed trial would compare the efficacy of the 300 mg netupitant/0.5 mg palonosetron combination vs. oral 0.5 mg palonosetron in terms of CR in the delayed phase (25-120 hours) in patients receiving MEC. Helsinn proposed this design to isolate the netupitant effect within the combination, since the NK_1 receptor antagonist was expected to be effective in the delayed phase of emesis. Key secondary efficacy endpoints would be CR in the acute (0-24 hours) and overall (0-120 hours) phases. The Division's response dated May 14, 2010 stated that the proposed approach for handling multiplicity due to multiple endpoints (the primary endpoint of CR delayed and key secondary efficacy endpoints of CR acute and CR overall) was acceptable.

In May 2010, Helsinn submitted a revised protocol for Study PALO-10-01 for special protocol assessment, a non-inferiority trial comparing oral 0.5 mg palonosetron to IV 0.25 mg palonosetron in patients receiving HEC. If successful, the proposed trial would demonstrate that oral palonosetron 0.5 mg is efficacious for the prevention of HEC in the acute phase (0-24 hours) and therefore contributes to the efficacy of the fixed combination. Superiority comparisons on CR in the delayed (25-120 hours) and overall (0-120 hours) phases between oral and IV palonosetron were not planned, since Helsinn was not seeking to claim that the palonosetron component of the combination was efficacious for the 25-120 hour and 0-120 hour phases. The Division's response dated June 18, 2010 stated that the proposed primary endpoint was acceptable, that the proposed secondary endpoints were deemed exploratory (b) (4) and that the proposed 15% non-inferiority margin was acceptable although type I error should be controlled at a two-sided 1% level for the results to be considered robust. The Division also stated that Study NETU-07-07, if successful, would be acceptable as the sole efficacy trial for the fixed combination supporting an indication for prevention of acute and delayed emesis in patients receiving HEC.

In September 2010, Helsinn resubmitted protocols for Study NETU-08-18 and Study PALO-10-01 for special protocol assessment. The Division issued agreement letters on November 3, 2010. The Division agreed that repeat cycle efficacy in Study NETU-08-18 could support labeling for repeat cycle efficacy for both MEC and HEC indications. The Division also agreed to the 15% non-inferiority margin for Study PALO-10-01 in patients receiving HEC, based on Helsinn's plan to use a 99% confidence interval. Helsinn did not pursue Study (b) (4) further.

The pre-NDA meeting was held on April 16, 2013. Helsinn planned to submit the results of several controlled trials to support the contribution of each component of the fixed combination to the claimed effect in patients receiving HEC (Study NETU-07-07 and PALO-10-01) and MEC (Study NETU-08-18) for one or more cycles as shown below:

Trial	Trial Population	Trial Objective	Emesis Phase of Interest	Design
NETU-07-07	HEC	Role of netupitant component	Delayed, Acute	Superiority of combination to oral palonosetron
PALO-10-01	HEC	Role of palonosetron component	Acute	Non-inferiority of oral to IV palonosetron
NETU-08-18	MEC*	Role of netupitant component	Delayed, Acute	Superiority of combination to oral palonosetron; Repeat cycle safety and efficacy
NETU-10-29	HEC and MEC	Role of netupitant/ palonosetron	Delayed, Acute	Repeat cycle safety and efficacy

*Oral palonosetron is already approved for prevention of acute emesis in patients receiving MEC

At the meeting, the Division noted that Study NETU 08-18, the sole efficacy trial supporting the MEC indication, enrolled patients receiving anthracycline and cyclophosphamide based chemotherapy. In light of ASCO's updated guideline on anti-emetics that reclassified regimens containing anthracyclines and cyclophosphamide from MEC to HEC[3], the Division stated that product labeling would describe the individual chemotherapeutic agents administered in Akynzeo clinical trials and would move beyond use of the older "MEC" classification.

Helsinn Healthcare SA submitted NDA 205718 for Akynzeo on September 26, 2013, which was received on September 27, 2013. The application was granted a standard review and was reviewed under the Program. Topics discussed at the Late Cycle Meeting held on June 11, 2014, included proposed wording of the indication statement in Akynzeo labeling, postmarketing clinical pharmacology studies to assess specific drug-drug interactions, and the applicant's pediatric development program.

FDA Advisory Committee Meeting. In the U.S., there are multiple 5-HT_3 receptor antagonists and one NK_1 receptor antagonist approved for the prevention of chemotherapy-induced nausea and vomiting. This application was not referred to an advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of disease, and outside expertise was not necessary.

Product Quality Considerations

The NDA applicant has provided sufficient information to assure the identity, strength, purity, and quality of Akynzeo, an oral fixed combination of two anti-emetics.

The drug product consists of a white-caramel hard gelatin capsule containing three immediate-release tablets each containing 100 mg of netupitant, and one soft gelatin capsule containing (b) (4) (b) (4) 0.56 mg of palonosetron hydrochloride (equivalent to 0.50 mg of palonosetron). Thus the dosage delivered by one Akynzeo capsule is 300 mg of netupitant and 0.5 mg of palonosetron.

Nonclinical Evaluation

[3] Basch E, Prestrud A, Hesketh P, et al. Antiemetics; American Society of Clinical Oncology Clinical Practice Guideline Update. JCO, 29:4189-4198, 2011.

Netupitant. Netupitant was not genotoxic in the Ames test, the mouse lymphoma cell mutation test, or the *in vivo* rat micronucleus test. Based on the treatment setting, i.e., patients receiving chemotherapy for treatment of malignancy, the Executive Carcinogenicity Assessment Committee determined that a carcinogenicity study need not be required. Netupitant had no effect on the fertility or reproductive performance of male and female rats.

Daily oral dosing of netupitant was assessed for up to 26 weeks in rats and 9 months in dogs. Netupitant induced phospholipidosis (in liver, lung, and lymphoid tissues) at doses of 10 mg/kg/day or higher in both rats and dogs. The calculated animal to human AUC multiples for netupitant, based on the AUC values associated with exposures to 10 mg/kg/day in both rats and dogs, ranged from 0.4 to 1.8. Oral toxicity studies with the combination of netupitant and palonosetron were performed in rats and dogs for up to 13 weeks. The combination did not produce any additional toxicity as compared to either drug alone. There was no evidence for adverse histologic cardiac effects in these studies.

Palonosetron. The applicant relied on and referenced its FDA-approved IV and oral palonosetron labeling (submitted under NDA 021372 and NDA 022233) to convey applicable palonosetron monotherapy mutagenicity, reproductive toxicity and carcinogenicity data in its labeling for the netupitant/palonosetron fixed combination.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian (CHO) cell forward mutation test, the *ex vivo* hepatocyte unscheduled DNA synthesis test, or the mouse micronucleus test. It was positive for clastogenic effects in the CHO cell chromosome aberration test.

Treatment with palonosetron was not tumorigenic in a 104-week carcinogenicity study in CD-1 mice. In a 104-week carcinogenicity study in Sprague-Dawley rats, however, treatment with palonosetron resulted in increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, palonosetron treatment produced hepatocellular adenoma and carcinoma, thyroid C-cell adenoma, and combined adenoma and carcinoma.

Palonosetron had no effect on the fertility or reproductive performance of male and female rats.

Clinical Pharmacology

Following oral administration of a single dose of Akynzeo, peak plasma concentrations were achieved in 5 hours for both netupitant and palonosetron.

Netupitant. There was a greater than dose-proportional increase in systemic exposure with dose increases from 10 to 300 mg, and a dose-proportional increase in systemic exposure with dose increases from 300 to 450 mg. The median half-life of netupitant in healthy subjects is 96 hours.

Netupitant is extensively metabolized primarily by CYP 3A4 to form a desmethyl derivative, M1, an N-oxide derivative, M2, and an OH-methyl derivative, M3. All three metabolites bind to the substance P/NK1 receptor. Peak concentration of M2 is achieved in 5 hours, while peak concentrations of M1 and M3 are achieved in 17-32 hours.

Palonosetron. Across the range of doses tested, C_{max} and systemic exposure were dose-proportional following administration of single oral doses in healthy subjects. The median half-life of palonosetron in healthy subjects is 44 hours.

In vitro studies have suggested that CYP 2D6, and to a lesser extent, CYP 3A4 and CYP 1A2, are involved in the metabolism of palonosetron. The two primary metabolites, N-oxide-palonosetron and 6-S-hydroxy-palonosetron each have less than 1% of the 5-HT_3 receptor antagonist activity of palonosetron.

Food effects. When Akynzeo is administered under fed conditions, the systemic exposures of netupitant and palonosetron were similar to those observed under fasting conditions.

QT prolongation potential. Co-administration of a single oral dose of 600 mg netupitant and 1.5 mg palonosetron had no significant QTc prolonging effects.

Effect of age. Overall, in clinical trials of Akynzeo in cancer patients, 18% were over 65 years of age. No substantial differences in safety or effectiveness were observed in these patients compared with younger patients. In cancer patients aged 29 to 75 years receiving Akynzeo, population PK analysis indicated that age did not influence the pharmacokinetic profiles of netupitant or palonosetron. In 12 healthy subjects over 65 years, mean systemic exposure and C_{max} were 25 and 36% higher, respectively, for netupitant, and 37 and 10% higher, respectively, for palonosetron compared to 22 healthy subjects aged 22 to 45 years.

Renal impairment. No dose adjustment for Akynzeo is necessary for patients with mild to moderate renal impairment. The effect of severe renal impairment on the pharmacokinetics of netupitant has not been studied, although severe renal impairment did not substantially affect the pharmacokinetics of palonosetron. The pharmacokinetic profiles of netupitant and palonosetron have not been studied in patients with end-stage renal disease requiring dialysis. Due to the large volume of distribution, dialysis is unlikely to be an effective treatment for Akynzeo overdose. Product labeling will recommend that the use of Akynzeo be avoided in patients with severe renal impairment or end-stage renal disease.

Hepatic impairment. No dose adjustment for Akynzeo is necessary for patients with mild to moderate hepatic impairment. There are limited data regarding the pharmacokinetic profiles of netupitant and palonosetron in patients with severe hepatic impairment; product labeling will recommend that use of Akynzeo should be avoided in these patients.

Drug interactions

Netupitant is a moderate inhibitor of CYP 3A4, and an inhibitor of P-gp and BCRP transporters. Product labeling will recommend that Akynzeo be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP 3A4 as the plasma concentrations of these medications may increase with co-administration of Akynzeo. Patients receiving concomitant dexamethasone, benzodiazepines, and chemotherapeutic agents metabolized by CYP 3A4 (including docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, and vinca alkaloids) should be carefully monitored.

Strong CYP 3A4 inhibitors. Once daily oral dosing of 400 mg ketoconazole, a strong inhibitor of CYP 3A4, altered the pharmacokinetics of the components of Akynzeo. The C_{max} and AUC of netupitant increased by 25 and 140%, respectively. The C_{max} and AUC of palonosetron increased by 15 and 10%, respectively. No dose adjustment for single dose administration of Akynzeo is recommended in product labeling.

CYP 3A4 inducers. Once daily oral dosing of 600 mg rifampicin, a strong inducer of CYP 3A4, altered the pharmacokinetics of the components of Akynzeo. The C_{max} and AUC of netupitant were reduced by 62% and 82%, respectively. The C_{max} and AUC of palonosetron decreased by 15 and 19%, respectively. Product labeling will recommend that use of Akynzeo in patients who are chronic users of strong CYP 3A4 inducers be avoided.

Postmarketing commitments. The applicant has agreed to conduct the following studies to further explore the potential for drug-drug interactions as post-approval commitments: 1) an *in vivo* study to evaluate the duration of Akynzeo inhibition on CYP 3A4 enzyme activity beyond four days, and 2) an *in vitro* study to evaluate the potential of netupitant to act as a substrate for the P-gp transporter in a bi-directional transport assay system.

Efficacy

Pivotal trials. Oral administration of Akynzeo (300 mg netupitant/0.5 mg palonosetron) was superior to oral 0.5 mg palonosetron in preventing acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy in two randomized, double-blind controlled trials.

The first trial (Study NETU-07-07) compared the efficacy of a single dose of oral Akynzeo (300 mg netupitant/0.5 mg palonosetron) with a single oral dose of 0.5 mg palonosetron, in cancer patients receiving a chemotherapy regimen that included cisplatin (median dose = 75 mg/m^2). Oral dexamethasone was also administered: 12 mg and 20 mg on day 1 to each group respectively, and 8 mg to both groups on days 2 to 4. Efficacy was assessed in 135 and 136 patients randomized to the two groups, respectively. Approximately half of participants were women, all were Caucasian and the median age was 53 years.

The key efficacy endpoint of interest was the proportion of patients with complete response (CR) defined as no emetic episode and no use of rescue medication for the 25-120 hours after the start of chemotherapy (delayed phase of emesis). Additional endpoints were CR for the 0-24 hours after the start of chemotherapy (acute phase of emesis), and CR for 0-120 hours after the start of chemotherapy (overall phase of emesis). A significantly greater proportion of patients responded to the combination of netupitant and palonosetron than to oral palonosetron alone in each of these emesis phases. Ninety percent of Akynzeo-treated patients experienced a CR in the delayed phase as compared to 80% of patients receiving oral palonosetron alone.

The second trial (Study NETU-08-18) compared the efficacy of a single dose of oral Akynzeo (300 mg netupitant/0.5 mg palonosetron) with a single oral dose of 0.5 mg palonosetron, in cancer patients receiving a chemotherapy regimen that included an anthracycline and cyclophosphamide. Oral dexamethasone was also administered: 12 mg and 20 mg on day 1 to each group respectively. No dexamethasone was administered on subsequent days. Efficacy was assessed in 724 and 725 patients randomized to the two groups, respectively. Most participants were Caucasian women and the median age was 54 years.

The primary efficacy endpoint was the proportion of patients with a CR in the delayed phase of emesis. The proportions of patients with a CR in the acute and the overall phases of emesis, respectively, were secondary endpoints. A significantly greater proportion of patients responded to the combination of netupitant and palonosetron than to oral palonosetron alone in each of these emesis phases. Seventy-seven percent of Akynzeo-treated patients experienced a CR in the delayed phase as compared to 70% of patients receiving oral palonosetron alone.

A multiple-cycle extension phase allowed for assessment of anti-emetic efficacy for a maximum of eight chemotherapy cycles. A total of 1275 patients completed cycle 2 and 388 completed cycle 6. During all chemotherapy cycles, the CR rate in the delayed phase was higher for Akynzeo-treated patients than for patients receiving oral palonosetron alone.

Additional controlled trials. In Study NETU-10-29, 309 patients undergoing initial and repeat cycles of chemotherapy, including highly emetogenic cisplatin-based chemotherapy, received Akynzeo. Efficacy was maintained in Akynzeo-treated patients throughout all chemotherapy cycles.

In Study PALO-10-01, a randomized, controlled, double-blind, non-inferiority trial, the efficacy and safety of a single dose of oral 0.5 mg palonosetron was compared to IV 0.25 mg palonosetron in cancer patients receiving highly emetogenic cisplatin ($\geq$70 mg/m^2) based chemotherapy. The purpose of this trial was to demonstrate that oral palonosetron at a dose of 0.5 mg is not inferior to IV 0.25 mg palonosetron, already approved for prevention of acute emesis in patients receiving HEC, and thereby contributes to the efficacy of the Akynzeo combination in these patients. A total of 370 and 369 patients were randomized to the two groups, respectively.

The primary efficacy endpoint was the proportion of patients with CR for the acute phase of emesis. In the oral palonosetron group, 89.4% of patients achieved a CR in the acute phase compared to 86.2% of patients in the IV palonosetron group, with a difference of 3.2% (99% CI: -2.7% to 9.2%). Non-inferiority of oral versus intravenous palonosetron was demonstrated since the lower limit of the two-sided 99% CI for the difference in proportions of patients with a CR was greater than the pre-defined non-inferiority margin set at -15%.

Safety

The safety of Akynzeo was assessed in 1169 cancer patients, including 782 exposed to Akynzeo for at least 4 cycles and 321 exposed for at least 6 cycles of chemotherapy. All patients received a single oral dose of Akynzeo 1 hour prior to the start of chemotherapy. In all studies, dexamethasone was co-administered. In patients receiving cisplatin-based highly emetogenic chemotherapy, the most common adverse reactions reported in association with Akynzeo treatment in cycle 1 were: dyspepsia and fatigue (in 4%), and constipation and erythema (in 3%).

In patients receiving anthracycline and cyclophosphamide based chemotherapy, the most common adverse reactions reported in association with Akynzeo treatment in cycle 1 were: headache (in 9%), asthenia (in 8%), and fatigue (in 7%). The safety profile in subsequent chemotherapy cycles was similar to that observed in cycle 1.

In a multi-cycle safety trial (Study NETU-10-29), the safety profile of Akynzeo was comparable to that of a combination of aprepitant and oral palonosetron in patients undergoing initial and repeat cycles (median 5 cycles, range of 1-14 cycles) of chemotherapy, including highly emetogenic chemotherapy.

Elevations in ALT, AST and/or bilirubin were noted in less than 1% of Akynzeo-treated and palonosetron-treated patients. Elevations were typically observed day 2 to 6 post-chemotherapy and resolved or improved in all patients with available follow-up values. The possibility that the chemotherapy contributed to these elevations cannot be ruled out.

Troponin monitoring was performed in both multi-cycle trials (Study NETU-08-18 and Study NETU-10-29). If a cTNI level ≥ 0.12 ng/ml was detected, patients had a cardiovascular functional assessment. If the cTNI level was ≥ 0.5 ng/mL a functional assessment was performed and the patient was withdrawn from the trial. The occurrence of elevations in troponin levels was low and there was no difference noted among patients receiving Akynzeo, oral palonosetron, or a combination of aprepitant and oral palonosetron. Most patients who had an elevated troponin level did not have a significant change in cardiac function, defined as a change in ejection fraction of <10%.

The ***Warnings and Precautions*** section of product labeling will include the serious risk of serotonin syndrome known to be associated with 5-HT_3 receptor antagonists. If symptoms of serotonin syndrome occur, product label will recommend that Akynzeo should be discontinued and supportive treatment be initiated.

Pregnancy Considerations

Akynzeo will be classified as a Category C drug, based on nonclinical findings for the netupitant component. Adequate and well-controlled studies with Akynzeo have not been conducted in pregnant women.

Netupitant. 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 3.7 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 3.7 times the human AUC at the recommended human dose during organogenesis through lactation produced no adverse effects in the offspring. However, a dose-dependent increase in adverse effects on embryo-fetal development (including

skeletal abnormalities) was observed in rabbit fetuses following daily administration of netupitant in pregnant rabbits during the period of organogenesis with doses at least 0.2 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy.

Palonosetron. 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.

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 Sprague-Dawley rats, 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.

Pediatric Considerations

Pediatric Use. The **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that the safety and effectiveness of Akynzeo have not been established in pediatric patients.

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new acting 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

FDA will defer the pediatric study requirement because Akynzeo is ready for approval for use in adults and the pediatric studies have not been completed. The deferred pediatric studies that will be required are:

1) an 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with netupitant alone;
2) a dose finding study to characterize the netupitant PK/PD relationship for complete response in the delayed phase following single oral dosing of netupitant and palonosetron (given concomitantly but in separate formulations) in pediatric cancer patients ages 0 to 17 years undergoing treatment with emetogenic chemotherapy, including highly emetogenic chemotherapy; and
3) a double-blind, randomized controlled study to evaluate the safety and efficacy of a dose of the netupitant/palonosetron fixed combination compared to standard therapy in pediatric cancer patients ages 0 to 17 years undergoing treatment with emetogenic chemotherapy, including highly emetogenic chemotherapy.

Tradename Review

The applicant's proposed tradename "Akynzeo" is acceptable from both a promotional and safety perspective. The applicant was informed of this determination on December 13, 2013.

Postmarketing Requirements under 505(o)

No postmarketing studies or trials will be required under Section 505(o) of the Federal Food, Drug, and Cosmetic Act.

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/s/

JULIE G BEITZ
09/29/2014