

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210493Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: March 27, 2018
From: Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: OPQ Review #1 of NDA 210493

Subject: Final Recommendation for NDA 210493

At the time when the OPQ Review #1 was completed on December 19, 2017, it had noted the following pending issues:

- The label/labeling issues were not completely resolved.

Because of these deficiencies, this NDA was not recommended for approval from the OPQ perspective.

The applicant submitted revised labels/labeling on January 09, 2018. The CMC sections of the immediate container label, carton label and package insert, were reviewed by Dr. Caroline Strassinger and found acceptable from the labeling perspective (see the attached labeling review).

Application Technical Lead's Assessment and Signature

The NDA is now recommended for **Approval** from the OPQ perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II

**Hitesh N.
Shroff -S**

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Memorandum

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

Date: 17-JAN-18

From: Caroline Strasinger, Ph.D.
Drug Product Reviewer
Branch V Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: Labeling Review #1 of NDA 210493

Subject: Finalized Label/labeling of CMC Sections

At the time when Labeling Review of this application was completed (11/28/2017), this NDA was not recommended for approval due to unresolved CMC labeling issues. On 01/09/2018, the applicant has submitted revised labeling which satisfactorily addressed all CMC labeling issues (see the **Attachment**).

Recommendation:

The previously noted CMC labeling issues have been satisfactorily resolved, and therefore, this application is now recommended for **approval** from the label/labeling perspective.

Caroline Strasinger, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

Attachment:

1. PI

Reviewer Comment: The Applicant has concurred with all recommendations to the labeling noted in the previous label/labeling review dated 28-NOV-2017. In the first labeling review, deficiencies were noted in Highlights, Section 3 Dosage Forms and Strength, Section 11 Description, and Section 16 How Supplied. The label (carton/container) was deemed adequate in review dated 28-NOV-2017. The Applicant provided the revised labeling on 09-JAN-2018; all Quality related sections of the labeling and the carton/container label have been provided below for completeness of the review.

a. **Highlights of Prescribing Information - ADEQUATE**

Product Title

AKYNZEO[®] (fosnetupitant and palonosetron) for injection, for intravenous use
Initial U.S. Approval: 201X

Dosage Forms and Strength

-----DOSAGE FORMS AND STRENGTHS-----

- Capsules: 300 mg netupitant/0.5 mg palonosetron
- For Injection: 235 mg fosnetupitant/0.25 mg palonosetron lyophilized powder in a single-dose vial for reconstitution (3)

b. **FULL PRESCRIBING INFORMATION**

#3 Dosage Forms and Strength – ADEQUATE

3 DOSAGE FORMS AND STRENGTHS

Capsules: 300 mg netupitant/0.5 mg palonosetron in a hard gelatin capsule with white body and caramel cap with “HE1” printed on the body.

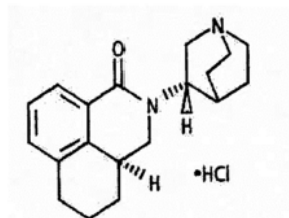
For Injection: 235 mg fosnetupitant/0.25 mg palonosetron white to off-white lyophilized powder in single-dose vial for reconstitution.

#11 Description – ADEQUATE

Only sections relevant to Akynzeo for injection are reproduced below:

Palonosetron hydrochloride is chemically described: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride. The empirical formula is

$C_{19}H_{24}N_2O \cdot HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:

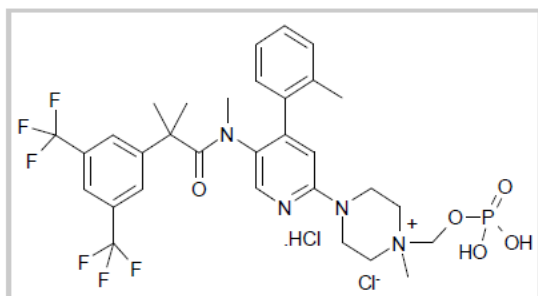


Netupitant is white to off-white crystalline powder. It is freely soluble in toluene and acetone, soluble in isopropanol and ethanol, and very slightly soluble in water.

Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

AKYNZEO (235 mg fosnetupitant/0.25 mg palonosetron) for injection is a (b) (4) combination product of fosnetupitant, a prodrug of netupitant, which is a substance P/neurokinin 1 (NK_1) receptor antagonist, and palonosetron hydrochloride, a serotonin-3 ($5-HT_3$) receptor antagonist.

Fosnetupitant chloride hydrochloride is chemically described as 2-(3,5-bis-trifluoromethylphenyl)-N-methyl-N-[6-(4-methyl-4-O-methylene-phosphatepiperazinium-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide chloride hydrochloride. The empirical formula is $C_{31}H_{36}F_6N_4O_3P \cdot Cl \cdot HCl$, with a molecular weight of 761.53. Fosnetupitant chloride hydrochloride exists as a single isomer and has the following structural formula:



Fosnetupitant chloride hydrochloride is white to off-white to yellowish solid or powder. Its solubility is pH dependent: at acidic pH (pH 2), its solubility is 1.4 mg/mL; at basic pH (pH 10), its solubility is 11.5 mg/mL.

Palonosetron hydrochloride is described above in this section.

AKYNZEO for injection is available for intravenous infusion, and is supplied as a sterile lyophilized powder in a single-dose vial. Each vial contains 235 mg of fosnetupitant (equivalent to 260 mg

fosnetupitant chloride hydrochloride) and 0.25 mg of palonosetron (equivalent to 0.28 mg of palonosetron hydrochloride). The inactive ingredients are edetate disodium (6.4 mg), mannitol (760 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment).

#16 How Supplied/Storage and Handling - ADEQUATE

16 HOW SUPPLIED/STORAGE AND HANDLING

Capsules

AKYNZEO (300 mg netupitant/0.5 mg palonosetron) capsules: hard gelatin capsules with white body and caramel cap with "HE1" printed on the body. They are supplied as follows:

NDC # 69639-101-01: pack of one capsule in one blister

NDC # 69639-101-04: pack of four capsules (two capsules per blister strip).

Storage

AKYNZEO capsules should be stored at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature].

For Injection

AKYNZEO (235 mg fosnetupitant/0.25 mg palonosetron) for injection: sterile, white to off-white lyophilized powder in single-dose vial for reconstitution.

NDC # 69639-102-01: pack of one vial

Storage

AKYNZEO for injection should be stored in carton, protected from light at 2° to 8°C (35.6 F to 46.4°F).

2. Labels - ADEQUATE

Reviewer Comment: The below label is provided for completeness of review. It was deemed adequate in the review dated 28-NOV-2017.

a. Container labels



b. Carton labels





Caroline
Strasinger

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Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 1/17/2018 10:53:40AM
GUID: 502d0913000029f9798ca689a802fa55

Recommendation: As of this review this 505 (b)(2) NDA is *not* ready for Approval in its present form per 21 CFR 314.125(b)(6).

**NDA 210493
OPQ Review #1**

Drug Name/Dosage Form	Akynzeo (fosnetupitant and palonosetron) for Injection
Strength	235 mg fosnetupitant/0.25 palonosetron lyophilized powder per vial
Route of Administration	Intravenous use
Rx/OTC Dispensed	Rx
Applicant	Helsinn Healthcare SA, Pazzallo-Lugano, Switzerland
US agent, if applicable	Dr. Craig Lehmann - August Consulting, Inc., Austin, TX

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	4/202017	OPQ
Amendment	7/06/2017	ONDP/DNDAPI
Amendment	7/19/2017	ONDP
Amendment	7/27/2017	ONDP/DNDAPI
Amendment	10/05/2017	ONDP/DNDAPI and OPF/DP/III/PABVIII
Amendment	10/13/2017	ONDP/DNDAPI and OPF/DP/III/PABVIII
Amendment	11/03/2017	OPQ/OPF/DMA/MAB
Amendment	11/28/2017	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Labeling	Caroline Strasinger	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Li Shan Hsieh	CDER/OPQ/OPF/ DPAIII/PABVIII
Microbiology	Lisa Shelton	OMPT/CDER/OPQ/OPF/DM A/MABI
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
Environmental Analysis (EA)	Caroline Strasinger	CDER/OPQ/ONDP/ DNDPII/NDPBV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	[REDACTED]	(b) (4)	Active	Dr. Joseph Leginus, September 25, 2017, adequate	LOA March 31, 2017
	Type II			Active	Dr. Joseph Leginus, May 08, 2017, adequate	LOA March 31, 2017
	Type III	[REDACTED]	(b) (4)	Active	Not reviewed, Information provided in NDA	LOA, June 30, 2015
	Type III			Active	Not reviewed, Information provided in NDA	LOA, April 01, 2015
	Type III			Active	Dr. Lisa Ashmore, November 09, 2017, Adequate	LOA, June 30, 2015

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	115191	Netupitant and Palonosetron for injection
NDA	205718	Akynzeo (netupitant and palonosetron) Capsules

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The Office of Process and Facilities (OPF) has made a final overall “Approval” recommendation for the facilities involved in this application as of this review.

The label/labeling issues have *not* been satisfactorily resolved.

Therefore, from the OPQ perspective, this NDA is *not* deemed ready for approval in its present form per 21 CFR 314.125(b)(6).

II. Summary of Quality Assessments

A. Product Overview

Akynzeo for injection contains fosnetupitant and palonosetron as active ingredients. Fosnetupitant is a prodrug of netupitant which is a substance P/neurokinin 1 (NK1) receptor antagonist and Palonosetron is a serotonin-3 (5-HT3) receptor antagonist antiemetic.

Akynzeo for injection is supplied as sterile, lyophilized powder for injection. Each single-dose vial contains 260 mg of fosnetupitant chloride hydrochloride equivalent to 235 mg of fosnetupitant free base and 0.28 mg of palonosetron hydrochloride, equivalent to 0.25 mg of palonosetron, and it also contains the following inactive ingredients; edetate disodium, mannitol, sodium hydroxide and/or hydrochloric acid (for pH adjustment). Akynzeo for injection must be reconstituted in 50 ml of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and administered as 30-minute infusion starting approximately 30 minutes prior to the start of chemotherapy.

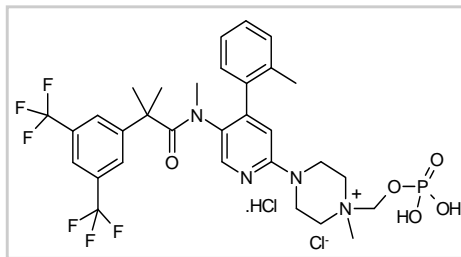
Proposed Indication(s) including Intended Patient Population	AKYNZEO for injection is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.
Duration of Treatment	As needed
Maximum Daily Dose	Recommended dosage in adults is one vial of Akynzeo for injection as an intravenous infusion over 30 minutes approximately 30 minutes prior to chemotherapy.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

Fosnetupitant chloride hydrochloride is a white to off-white to yellowish hygroscopic solid. It is an achiral compound and produced as (b) (4) with the proposed manufacturing process. It is soluble in water and alcohol. Its solubility in water is pH dependent. It is more soluble at higher pH. It is manufactured by Helsinn Advanced Synthesis SA, Switzerland. The complete CMC information is provided in DMF (b) (4) from the manufacturer. This DMF was reviewed by Dr. Joseph Leginus on September 25, 2017 and was deemed adequate.

Fosnetupitant chloride hydrochloride is chemically described as 2-(3,5-bis-trifluoromethylphenyl)-N-methyl-N-[6-(4-methyl-4-O-methylene-phosphatepiperazinium-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide chloride hydrochloride. The empirical formula is $C_{31}H_{36}F_6N_4O_5P \cdot Cl \cdot HCl$, with a molecular weight of 761.53.



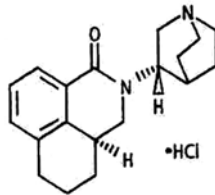
The quality of fosnetupitant chloride hydrochloride is controlled by its specification which includes appearance, identification by infrared spectroscopy and HPLC; purity by HPLC, impurities by HPLC and (b) (4), etc. (b) (4) are also included in the specification. The API specification deemed adequate per drug substance reviewer, Dr. Joseph Leginus. (See **the Drug Substance** review). Based on fosnetupitant chloride hydrochloride stability data provided in DMF (b) (4), a re-test period of (b) (4) months at (b) (4) was established.

Fosnetupitant chloride hydrochloride is a pro-drug of netupitant. It is hypothesized that *in-vivo* fosnetupitant chloride hydrochloride is hydrolyzed to give (b) (4) netupitant.

Palonosetron hydrochloride, USP is a white to off-white crystalline powder. It is a chiral compound containing two chiral centers. It is manufactured by Helsinn Advanced Synthesis SA, Switzerland (b) (4). The complete CMC information is provided in DMF (b) (4) from the manufacturer. This DMF was reviewed by Dr. Joseph Leginus on May 08, 2017 and was deemed adequate.

Palonosetron hydrochloride is chemically described: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride.

The empirical formula is $C_{19}H_{24}N_2O \cdot HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride has the following structural formula:



The quality of palonosetron hydrochloride is controlled by its specification which includes appearance, identification by infrared and UV spectroscopy; purity by HPLC, (b) (4)

The API specification deemed adequate per drug substance reviewer, Dr. Joseph Leginus. (See **the Drug Substance** review).

The Office of Process and Facilities (OPF) reviewer, Dr. Michael Klupal has made an "Adequate" recommendation for manufacturing and testing facilities of both drug substances (See the **Facilities** review).

Both APIs are manufactured by Helsinn Advanced Synthesis SA, Switzerland and controlled to conform to the requirements (specification) to produce Akynzeo for injection.

Drug Product:

Akynzeo for injection is supplied as a sterile, white to off-white lyophilized (b) (4) powder in a single-dose vial for intravenous use. The clear glass vial is stoppered with rubber stopper and capped with aluminum seal with (b) (4) disc.

Each vial of Akynzeo for injection contains 260 mg fosnetupitant chloride hydrochloride salt equivalent to 235 mg fosnetupitant, and 0.28 mg palonosetron hydrochloride equivalent to 0.25 mg palonosetron as active ingredients, and also the following inactive ingredients; edetate disodium (b) (4) mannitol and sodium hydroxide or hydrochloric acid (for pH adjustment). It is supplied as a single-dose vial. The drug product does not contain any preservatives or antioxidants.

The drug product is manufactured by Patheon Italia S.p.A., Monza, Italy. The manufacturing process consists of typical (b) (4) (u) () steps.

The drug product manufacturing process was reviewed by Dr. Li-Shan Hsieh and was deemed acceptable. (See **Process** review)

The overall control strategy for the drug product is deemed adequate based on raw material controls, drug product specification including appearance, assay, impurities, (b) (4), dose uniformity, particulate matter, sterility, pH, container closure integrity and bacterial endotoxin limits. For assay and impurities determinations, the applicant developed and used non-compendial, validated in-house methods.

Based on long-term and accelerated stability data of the drug product assuring the identity, strength, purity and quality, a 24-month of expiration dating period when stored at refrigerated temperature ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$) in the proposed container closure system is granted. (See the **Drug Product** review of Dr. Caroline Strasinger). The reconstituted solution in 0.9% sodium chloride, USP or 5% dextrose, USP should be used within 3 hours of reconstitution.

The environmental monitoring a (b) (4) manufacturing process buildings/facilities, component/ equipmen (b) (4) as well as the microbiology related attributes in the drug product specification including endotoxins, sterility and container closure integrity etc. were reviewed by Dr. Lisa S.G. Ashmore and recommended this NDA for approval based on sterility assurance. (See the **Microbiology** review).

The Office of Process and Facilities (OPF) reviewer, Dr. Michael Klupal, has made an “Adequate” recommendation for the drug substances and drug product manufacturing and testing facilities (See the **Facility** review).

An environmental impact analysis assessment with calculation of estimated entry into aquatic environment, less than 1 ppb, was provided with a statement that no extraordinary circumstances exist. Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31 was deemed acceptable.

The labels and labeling issues are *not* satisfactorily resolved from the CMC perspective according to the labeling reviewer, Dr. Caroline Strasinger. Therefore, this application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the OPQ perspective until the deficiencies listed below are satisfactorily resolved. (See the **Labeling** review).

C. Lifecycle Management Consideration (NDA only)

(b) (4)

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies:

The following labeling comments should be resolved with the applicant.

A. Regarding PI

a) Highlight Section

- Modify Dosage Forms and Strength in the highlights to: For injection: 235 mg fosnetupitant/0.25 mg palonosetron, (b) (4) lyophilized powder, (b) (4) in a single dose vial for reconstitution

b) Full Prescribing Information**#3: Dosage Forms and Strengths**

- Modify the injection portion of dosage forms and strengths to the following:
For Injection: 235 mg fosnetupitant/0.25 mg palonosetron white to off-white lyophilized powder in single-dose vial for reconstitution.

#11: Description

- Alter the formula for fosnetupitant chloride hydrochloride to $C_{31}H_{36}F_6N_4O_5P \cdot Cl \cdot HCl$
- Modify the solubility statement to that which is supported by data
- Editorial changes are needed as described in the text to improve clarity.

#16: How Supplied/Storage and Handling

- Include a statement to store in carton and protect from light.
- Delete (b) (4) statement.
- Delete the (b) (4)

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
December 15, 2017

Hitesh N.
Shroff -S

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LABELING

R. Regional Information

1.14 Labeling

The Labeling for this NDA is being combined with the already approved Label for Akynzeo® (netupitant and palonosetron) capsules. Only the Akynzeo® (fosnetupitant and palonosetron) for injection is being reviewed below, as the other labeling information is already approved and will not be modified.

Also during this review cycle, the USAN name of fosnetupitant chloride will be rescinded and changed to fosnetupitant chloride hydrochloride on November 29, 2017. This name better aligns with the structure and molecular weight of the drug substance. In Section 11: Description, the applicant has proposed fosnetupitant chloride hydrochloride and therefore no edits are necessary, however the carton incorrectly used fosnetupitant chloride in the equivalency statement. As such the name has been revised to fosnetupitant chloride hydrochloride for the carton only.

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

Akynzeo® (fosnetupitant and palonosetron) for injection, for intravenous use
U.S. Approval: 201X

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Akynzeo Established Name: (fosnetupitant and palonosetron) for injection	Adequate
Dosage form, route of administration	Dosage: for injection Route: Intravenous	Adequate
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		

Summary of dosage form and strength	For injection: 235 mg fosnetupitant/0.25 mg palonosetron	Adequate

2) DOSAGE FORMS AND STRENGTHS

For injection: 235 mg fosnetupitant/0.25 mg palonosetron (b) (4) lyophilized powder (b) (4) in a single dose vial for reconstitution (3)

Reviewer Assessment: INADEQUATE

Applicant should modify the text of the dosage forms and strengths of the highlights for clarity as noted above. This information was communicated to OND on October 17, 2017 and will be communicated to the Applicant on December 14, 2017.

2. "FULL PRESCRIBING INFORMATION

#3: DOSAGE FORM AND STRENGTHS

3 DOSAGE FORMS AND STRENGTHS

Capsules: 300 mg netupitant/0.5 mg palonosetron in a hard gelatin capsule with white body and caramel cap with "HE1" printed on the body.

For Injection: 235 mg fosnetupitant/0.25 mg palonosetron (b) (4) white to off-white lyophilized powder (b) (4) (b) (4) in single-dose vial for reconstitution.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	For Injection	Adequate
Strengths: in metric system	For injection: 235 mg fosnetupitant/0.25 mg palonosetron	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	235 mg/0.25 mg	Adequate Although no equivalency statement is made, since that statement is made in the Description section as well as container and carton labels, it is deemed acceptable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White to off-white lyophilized powder in single-dose vial	Adequate

Reviewer Assessment: **Inadequate**

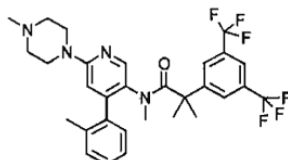
Applicant should modify the text of the dosage forms and strengths for clarity as noted above. This information was communicated to OND on October 17, 2017 and will be communicated to the Applicant on December 14, 2017.

#11: DESCRIPTION

11 DESCRIPTION

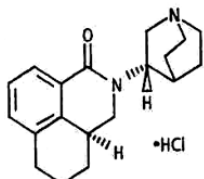
AKYNZEO (300 mg netupitant/0.5 mg palonosetron) capsules are an oral combination product of netupitant, a substance P/neurokinin 1 (NK₁) receptor antagonist, and palonosetron hydrochloride, a serotonin-3 (5-HT₃) receptor antagonist. Both netupitant and palonosetron hydrochloride are anti-nausea and anti-emetic agents.

Netupitant is chemically described: 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl]propanamide. The empirical formula is C₃₀H₃₂F₆N₄O, with a molecular weight of 578.61. Netupitant exists as a single isomer and has the following structural formula:



Palonosetron hydrochloride is chemically described: (3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride. The empirical formula is

C₁₉H₂₄N₂O·HCl, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:



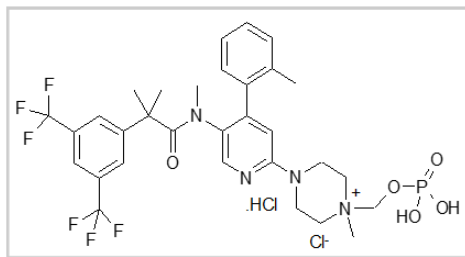
Netupitant is white to off-white crystalline powder. It is freely soluble in toluene and acetone, soluble in isopropanol and ethanol, and very slightly soluble in water.

Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

Each AKYNZEO capsule is composed of one white-caramel hard gelatin capsule which contains three tablets each containing 100 mg netupitant and one gelatin capsule containing 0.5 mg palonosetron (equivalent to 0.56 mg palonosetron hydrochloride). The inactive ingredients are butylated hydroxyanisole (BHA), croscarmellose sodium, gelatin, glycerin, magnesium stearate, microcrystalline cellulose, mono- and di-glycerides of capryl/capric acid, polyglyceryl dioleate, povidone K-30, purified water, red iron oxide, silicon dioxide, sodium stearyl fumarate, sorbitol, sucrose fatty acid esters, titanium dioxide and yellow iron oxide. It may contain traces of medium-chain triglycerides, lecithin, and denatured ethanol.

AKYNZEO (235 mg fosnetupitant/0.25 mg palonosetron) for injection is a combination product of fosnetupitant, a prodrug of netupitant which is a substance P/neurokinin 1 (NK₁) receptor antagonist, and palonosetron hydrochloride, a serotonin-3 (5-HT₃) receptor antagonist.

Fosnetupitant chloride hydrochloride is chemically described as 2-(3,5-bis-trifluoromethylphenyl)-N-methyl-N-[6-(4-methyl-4-O-methylene-phosphatepiperazinium-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide chloride hydrochloride. The empirical formula is C₃₁H₃₆F₆N₄O₃·P·Cl·HCl, with a molecular weight of 761.53. Fosnetupitant chloride hydrochloride exists as a single isomer and has the following structural formula:



Fosnetupitant chloride hydrochloride is white to /off-white to yellowish solid or powder. Its solubility is pH dependent: at acidic pH (pH 2), its solubility is 1.4 mg/mL; at (b) (4) basic pH (pH 10), its solubility is 11.5 mg/mL; (b) (4)

Palonosetron hydrochloride is described above in this section.

(b) (4) AKYNZEO for injection is supplied as a sterile lyophilized powder in a single-dose vial. Each vial contains 235 mg of fosnetupitant (equivalent to 260 mg fosnetupitant chloride hydrochloride) and 0.25 mg of palonosetron (equivalent to 0.28 mg of palonosetron hydrochloride). The inactive ingredients are edetate disodium (6.4 mg), mannitol (760 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment).

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	Akynzeo (fosnetupitant and palonestron) for injection	Adequate
Dosage form and route of administration	For injection	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	235 mg of fosnetupitant (equivalent to 260 mg fosnetupitant chloride hydrochloride) and 0.25 mg of palonosetron (equivalent to 0.28 mg of palonosetron hydrochloride).	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	edetate disodium (6.4 mg), mannitol (760 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment)	Adequate
Statement of being sterile (if applicable)	Sterile	Adequate
Pharmacological/ therapeutic class	substance P/neurokinin 1 (NK1) receptor antagonist	Adequate
Chemical name, structural formula, molecular weight	Structure, molecular weight, formula presented	INADEQUATE, formula modification noted above
If radioactive, statement of important nuclear characteristics.	NA	Adequate
Other important chemical or physical properties (such as pKa or pH)	Solubility is pH dependant	INADEQUATE, original solubility statement was unfounded. Has been modified to what can be supported by D.S. Review.

Reviewer Assessment: INADEQUATE

Applicant should alter the formula for fosnetupitant chloride hydrochloride to

C₃₁H₃₆F₆N₄O₅P•Cl•HCl and modify the solubility statement to that which is supported by data.

Additional edits noted above of the Description should be made for clarity. This information was communicated to OND on October 17, 2017 and will be communicated to the Applicant on December 14, 2017.

#16: HOW SUPPLIED/STORAGE AND HANDLING

16 HOW SUPPLIED/STORAGE AND HANDLING

Capsules

AKYNZEO (300 mg ~~netupitant~~/0.5 mg palonosetron) capsules: hard gelatin capsules with white body and caramel cap with "HE1" printed on the body. They are supplied as follows:

NDC # 69639-101-01: pack of one capsule in one blister

NDC # 69639-101-04: pack of four capsules (two capsules per blister strip).

Storage

AKYNZEO capsules should be stored at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature].

For Injection

AKYNZEO (235 mg fosnetupitant/0.25 mg palonosetron) for injection: sterile, white to off-white lyophilized powder (b) (4) in single-dose vial for reconstitution.

NDC # 69639-102-01: pack of one vial

Storage

AKYNZEO for injection should be stored in carton, protected from light at 2° to 8°C (35.6 F to 46.4°F)

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	235 mg/0.25 mg palonosetron for injection	Adequate
Available units (e.g., bottles of 100 tablets)	Pack of one vial	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to off-white lyophilized powder	Adequate
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	Missing that it should be protected from light	INADEQUATE Add a statement in carton, that it should be protected from light
Storage conditions	2 to 8°C	INADEQUATE delete (b) (4) 
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by Helsinn Birex Pharmaceuticals Distributed by Helsinn Therapeutics, Inc	Adequate

Reviewer Assessment: INADEQUATE

Applicant should include a statement to store in carton and protect from light, alter the temperature conditions and modify the text of the How Supplied/Storage and Handling for clarity as noted above. This information was communicated to OND on October 17, 2017 and will be communicated to the Applicant on December 14, 2017.

II. Labels (Provided January 12, 2017)

1. IMMEDIATE CONTAINER LABEL

Reviewer Assessment: ADEQUATE per the revised label provided on November 28, 2017 (see page 8).

The label provided on January 12, 2017 was inadequate based on the listed deficiencies below. This information was communicated to the applicant October 2017.

Label provided January 12, 2017



- Correct name and strength presentation to the below. Strength should appear directly below the name:
Akynzeo®
(fosnetupitant and palonosetron) for injection
235 mg and 0.25 mg
- Change text to “Sterile for Intravenous Infusion Only”
- Include a side panel of
Each vial contains:
Fosnetupitant.....235 mg
(equivalent to 260 mg fosnetupitant chloride hydrochloride)
Palonosetron.....0.25 mg
(equivalent to 0.28 palonosetron hydrochloride)
- Add a Barcode

- Insert a degree symbol between 2 and C and correct parenthetical to (36°F – 46°F) (it is suggested this is added to side panel)
- Add protect from light (it is suggested this is added to side panel)

On November 28, 2017 the applicant responded with the following revised label and is reviewed below. The November 28, 2017 provided label is **ADEQUATE.**

(b) (4)



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Akynzeo (fosnetupitant and palonosetron)	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	235 mg/0.25 mg per vial	Adequate
Net contents	235 mg and 0.25 mg per vial	Adequate
“Rx only” displayed prominently on the main panel	Rx only	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Present	Adequate
Lot number and expiration date (21 CFR 201.17)	Location present	Adequate
Storage conditions Special handling, e.g., “Dispense in tight and light resistant container as defined in USP”.	Store in refrigerator 2°C-8°C (36°F-46°C); Protect from light. Store in carton.	Adequate
Bar code (21CFR 201.25)	Included	Adequate
Name of manufacturer/distributor	Distributor is present	Adequate
And others, if space is available		

2. CARTON LABELS:

Reviewer Assessment: ADEQUATE per the revised label provided on November 28, 2017 (see page 11).

The carton label provided on January 12, 2017 below was inadequate based on the listed deficiencies. This information was communicated to the applicant October 2017.

Label provided January 12, 2017

Several deficiencies with the carton are noted above in the diagram and the comments are notated below. These deficiencies directly relate to Quality review of the label.

- The font size of the established name must be greater than 50% of the trade name.
- SC1: Arrange alphabetically to be consistent with the PI
- SC3: Include the strength on the primary display panels (red text has been inserted by the reviewer)
- SC4: Modify (b) (4) to preferred text of “1 single dose vial”
- SC6: Remove (b) (4) as a manufacturer (Patheon is the only manufacturer in the application. (b) (4) (b) (4) but not a manufacturer)

On November 28, 2017 the applicant responded with the following revised carton label and it is reviewed below. The November 28, 2017 provided label is **ADEQUATE.**



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	Akynzeo (fosnetupitant and palonosetron) for injection	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	Equivalency present and in proper format	Adequate
Net quantity of dosage form	1 single dose vial	Adequate
"Rx only" displayed prominently on the main panel	Displayed on front; suggest adding to back panel as well	Adequate
Lot number and expiration date	Inside flap	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store in refrigerator 2°C-8°C (36°F-46°C); Protect from light. Store in carton.	Adequate
Bar code (21CFR 201.25)	Side panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Front and back panel	Adequate
Manufacturer/distributor's name	Back and Side panel	Adequate
Quantitative ingredient information (injectables)	Edetate sodium (b) (4) 6.4 mg, Mannitol 760 mg, Sodium hydroxide and/or hydrochloric acid (for pH adjustment)	Adequate
Statement of being sterile (if applicable)	Sterile	Adequate
"See package insert for dosage information"	Front panel. Read accompanying directions also appears on side and back panel	Adequate
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Not applicable	Adequate

III. LIST OF DEFICIENCIES:

A. Regarding PI

a) **Highlight Section**

- Modify Dosage Forms and Strength in the highlights to: For injection: 235 mg fosnetupitant/0.25 mg palonosetron, (b) (4) lyophilized powder (b) (4) in a single dose vial for reconstitution

b) **Full Prescribing Information**

#3: Dosage Forms and Strengths

- Modify the injection portion of dosage forms and strengths to the following:
For Injection: 235 mg fosnetupitant/0.25 mg palonosetron white to off-white lyophilized powder in single-dose vial for reconstitution.

#11: Description

- Alter the formula for fosnetupitant chloride hydrochloride to $C_{31}H_{36}F_6N_4O_5P \cdot Cl \cdot HCl$
- Modify the solubility statement to that which is supported by data
- Editorial changes are needed as described in the text to improve clarity.

#16: How Supplied/Storage and Handling

- Include a statement to store in carton and protect from light.
- Delete (b) (4) statement.
- Delete the (b) (4)

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

The Label and Labeling of NDA 209296 is inadequate due to the deficiencies noted above for Highlights, Section 3, 11 and 16 of the PI. This information was communicated to OND on October 12, 2017 and will be communicated to the Applicant on December 14, 2017.

This application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the label/labeling perspective until the deficiencies noted above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

***Caroline Strasinger, PhD 28-NOV-2017
OPQ, ONDP, DNDP II, BV***

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Strasinger's assessment on the labeling and labels and concur with her recommendation that this application is **not** deemed ready for approval as of this review.

***Moo-Jhong Rhee, Ph.D. 28-NOV-2017
Chief, Branch V
DNDP II/ONDP***

MICROBIOLOGY

Product Background

NDA: 210493

Drug Product Name / Strength: Akynzeo (fosnetupitant + palonosetron HCl) / 235 mg fosnetupitant + 0.25 mg palonosetron

Route of Administration: Intravenous infusion

Applicant Name: Helsinn Healthcare SA

Manufacturing Site:

Patheon Italia S.p.A.
 Viale Gian Battista Stucchi, 110
 20900 Monza
 Italy

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Review Summary:

- The submission is **recommended** for approval on the basis of sterility assurance.
- (b) (4)

List Submissions Being Reviewed:

Submit	Received	Assigned to Reviewer
04/20/17	04/20/17 (SD#1)	04/25/17
07/06/17	07/06/17 (SD#6) ^a	N/A
11/03/17	11/03/17 (SD#27) ^a	11/07/17

^a Response to Quality Information Request (IR) including Microbiology

Highlight Key Outstanding Issues from Last Cycle: N/A. This is a first cycle review.

Remarks: The subject of review is submitted electronically (eCTD). Some tables in this review are excerpted from the electronic submission. All references to Module, Section, and pdf documents in this review are from the NDA submission dated 04/20/17 except where noted otherwise.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: DMF (b) (4) (Type V) and associated microbiology review
D19418M05R01.docx, 11/09/17, L. Ashmore– (b) (4)

List Number of Comparability Protocols (ANDA only): N/A

Filename: N210493MR01.docx

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

For Batch Nos. 361285-00001, 361435-00001, and 361435-00002, acceptable results are reported (to-date) for container/closure integrity, BET, sterility test for the following storage conditions/time points:

- Accelerated (25°C±2°C/60%RH±5%RH), T = 0 months
- Long-term (2°C-8°C/ambient humidity), T = 0 and 12 months

Reviewer's Assessment: *Adequate*

A Appendices

A.2 Adventitious Agents Safety Evaluation – N/A

Reviewer's Assessment: *N/A*

A.2.1 Materials of Biological Origin

Reviewer's Assessment: *N/A*

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: *N/A*

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: *N/A*

A.2.4 Viral Clearance Studies

Reviewer's Assessment: *N/A*

R Regional Information

Executed Batch Records

Executed lot #: 361285-00001

The executed batch record confirms that validated (b) (4) manufacturing processes were used for the manufacture of the exhibit batch.

The proposed master batch record for commercial production is not provided.

Reviewer's Assessment: *Adequate*

Comparability Protocols – No CP was included in the application.

Reviewer's Assessment: *N/A*

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

Storage temperature: (b) (4) °C

Route of administration: IV infusion

Container: Single dose vial

Reconstituted/Further Diluted Drug Product

- Pre-use storage: (b) (4) °C
- Reconstitution: 20 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP is aseptically injected into the vial. The entire volume is withdrawn and transferred to an infusion vial or bag containing 30 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP to yield a total volume of 50 mL.
- The total time from reconstitution to start of infusion should not exceed 3 hours. The reconstituted solution and the final diluted solution are stored at room temperature.
- The final solution is administered over a 30-minute infusion.
- **Post-dilution/constitution hold time** – The applicant states that microbial testing is not performed since the product is a single use product and administered at the time of reconstitution (3.2.P.2.5, pharmaceutical-development-10.pdf, p. 1 of 1).

Reviewer's Assessment: *Adequate*

Post-Approval Commitments: *N/A*

List of Deficiencies: *N/A*

Primary Microbiology Reviewer Name and Date: **Lisa S.G. Ashmore, Ph.D., 11/09/17**

Secondary Reviewer Name and Date (and Secondary Summary, as needed): **Bryan S. Riley, Ph.D., 11/09/17**



**METHOD VERIFICATION
REPORT SUMMARY**

Date: December 15, 2017

To: Caroline Strasinger, Drug Product Reviewer
Joseph Leginus, Drug Substance Reviewer
Hitesh Shroff, CMC Lead
Oumou Barry, RBPM

Through: Jason Rodriguez, Ph.D., Lab Chief, Branch I, CDER/OPQ/OTR/DPA

From: Salwa Poole, Chemist, Ph.D., Chemist, ORA/DET-CHEM
Bruce Harris, Ph.D., Interdisciplinary Scientist, ORA/ORS
Tim Andres Marzan, Chemist, CDER/OPQ/OTR/DPA
Laura Pogue, Ph.D., Method Verification Coordinator,
CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 210493:
AKENZYO (Fosnetupitant- Palonosetron Powder for Infusion) 260 mg/vial

The following methods were evaluated and are acceptable for quality control and regulatory purposes with modifications as described in the comments below:

1. NDA 210493, (b) (4) Identification by IR
2. NDA 210493, (b) (4) Identification, Purity and Assay by HPLC
3. NDA 210493, Reconstitution Time
4. NDA 210493, HPLC 08-PNET, Fosnetupitant Identification, Assay and Related Substances by HPLC/UV

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the methods:

1. The calculation for the % Recovery of the check standards (T2, T1_{ctrl} and T1_{last}) in the Drug Product HPLC assay method is not specified in the method. The % Recovery was calculated as follows:

% Recovery = (b) (4)

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2. The identification of the [REDACTED] (b) (4) peaks and other related substances peaks are based on the approximate relative retention times and pattern of the chromatogram. Variation of the retention times observed between sequences could lead to misidentification of the peaks. Refer to section 10.2 of the Drug Product related substances determination method. [REDACTED] (b) (4) are quantitated using a different method. [REDACTED] (b) (4) has a specification limit of [REDACTED] (b) (4) compared with [REDACTED] (b) (4) specification limit for all other impurities. **DPA suggests** inclusion of a retention time ID standard for [REDACTED] (b) (4) in the injection sequence.

Original analyst worksheets can be viewed using this ECMS link:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8817ea95f>

Summary of Analysis

1. (b) (4), Identification by IR: Pass

The spectrum of the standard matches the spectrum of the sample.

2. (b) (4) Identification, Purity and Assay by HPLC Identification: Pass

(Specification: (b) (4))

(b) (4)

RT STD: (b) (4)

(b) (4)

(b) (4)

Purity:

Peak	RRT	% Impurity	Average (2) % Impurity	Reporting (b) (4)	Reporting (b) (4)	Results
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	pass
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	pass
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	pass
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	pass
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	pass
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	pass
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	pass

Assay:

Assay by HPLC	Average	Specifications	Results
% Label Claim=98.5, 98.6	98.6	NLT (b) (4)%	Pass

3. Reconstitution Time (in seconds): Pass

Vial 1	Vial 2	Vial 3	Vial 4	Vial 5	Average	Specification
23	18	27	19	22	21.8	(b) (4)

4. HPLC 08-PNET, Fosnetupitant Identification, Assay and Related Substances by HPLC/UV: Pass

The original analysis for the drug product related substances determination slightly failed the system suitability for the blank injection (b) (4)

(b) (4) Therefore, a check analysis was performed. This analysis passed system suitability and a second set of results for the drug product was

NDA 210493

generated. Both sets of results met all specifications. Refer to the Original and Check Analysis results below.

Original Analysis

Fosnetupitant ID: Pass

The chromatograms of each sample at (b) (4) show a major peak at the same retention time as for the ID reference solution. The UV spectrum of the major peak in each sample show a profile similar to the reference UV spectrum.

Assay:

Assay by HPLC	Sample 1	Sample 2	Sample 3	Average	Specifications	
% Label Claim	103.9	103.7	102.9	103.5	(b) (4)	Pass

Impurity:

Peak	RRT	Sample 1 % Impurity	Sample 2 % Impurity	Sample 3 % Impurity	Average (3) % Impurity	Reporting Limits	Results
(b) (4)							pass
							pass
							pass
							pass
							pass
							pass
							pass

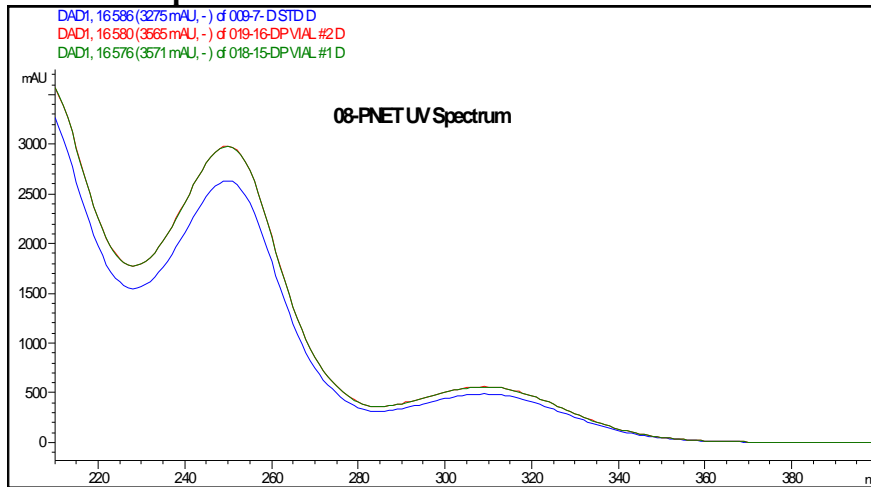
Check Analysis

Fosnetupitant Identification:

By Retention Time Comparison - Pass

Sample #	Area	Ret Time (min)	Specification	Pass/Fail
Vial #1	2751.49	16.577	(b) (4) min.	Pass
Vial #2	2763.48	16.579	min.	Pass

By UV Spectrum Comparison – Pass



Assay:

Sample #	Area	Assay (mg/vial)	Label Claim (mg/vial)	% Label Claim	Specification	Pass/Fail
Vial #1	2751.49	269.19	260	103.5	(b) (4) %	Pass
Vial #2	2763.48	270.37	260	104.0	%	Pass
Average		269.78		103.8	%	Pass

Related Substances:

Name	RRT	Vial #1	Vial #2	Average	Report	Pass/Fail
(b) (4)						Pass
						Pass
						Pass
						Pass

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 210493

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay	Formulation, Raw materials, Process Parameters, Scale/equipment	L	(b) (4)	The dose strength of the drug product is expected to be within the specification during the entire shelf life from product quality perspective. None	None
Impurities	Raw materials, process parameters,	M		The degradation/impurities of the drug product are expected to be controlled and the drug product is safe for IV administration during the entire shelf life from product quality perspective. Low	(b) (4)
Bioburden	Manufacturing environment and processes	M		Bioburden is controlled in the drug product (b) (4) Low	None
Sterility	Sterilization	M		Sterility is controlled in drug product at (b) (4). Low	None