CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205718Orig1s000

CHEMISTRY REVIEW(S)

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: September 16, 2014

FROM: Raymond P. Frankewich, Ph.D., Review Chemist, Branch IV, DNDQA II/ONDQA

THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, DNDQA II/ONDQA

TO: CMC Review #1 for NDA 205718

SUBJECT: Clarification of CMC Review #1 of NDA 205718

In CMC Review #1, dated 5-29-2014, Table 3 on pg. 49 needs to be revised.

In the table, three substances, (b) (4) Polyglyceryl oleate (b) (4) and Sodium Stearyl Fumarate NF are noted as **not being present** in the Inactive Ingredient Database (IIG):

However, in fact, all three of these substances are listed in the IIG.

(b) (4) and polyglyceryl oleate are listed under different names as shown in the following tables.

Substances Listed in IIG Consistent with (b) (4) ,,

(b) (4)

Substances Listed in IIG Consistent with "polyglyceryl oleate"

(b) (4)

It is noted that the amounts of these substances listed in the IIG are greater than the amounts that are used in the drug product, AKYNZEO® (netupitant and palonosetron) capsules. A revised Table 3 is provided below. Revisions to the table are highlighted.

In CMC Review #1, it was concluded that the levels of [redacted] and polyglyceryl oleate used in the drug product was not considered a safety issue, because these were also used in the previously approved drug, Aloxi® (NDA 22-233), and that conclusion remains valid.

The specific polyglyceryl oleate used in this drug product [redacted] is identified on the website of its supplier [redacted] The maximum amount in the table below is the maximum for [redacted]

Table 3 – Excipients in the NPCC, Daily Intake, and Current Levels of Intake from Inactive Ingredient Database

Excipient	Reference	Function	Amount per day (one capsule) (mg)	Database[1] maximum per capsule[2] (mg)
Microcrystalline cellulose [redacted]	NF/Ph. Eur	[redacted]	[redacted]	[redacted]
Sucrose [redacted] acid esters	Internal			
Povidone K-30	USP/Ph. Eur.			
Croscarmellose sodium	NF / Ph. Eur.			
Silicon dioxide [redacted]	NF / Ph. Eur.			
Sodium stearyl fumarate	NF / Ph. Eur.			
Magnesium stearate [redacted]	NF / Ph. Eur.			
[redacted]	Ph. Eur.			
Glycerin [redacted]	USP/Ph. Eur.			
Polyglyceryl oleate [redacted]	Internal			
Butylated hydroxyanisole (BHA)	NF / Ph. Eur.			

1 - FDA Inactive Ingredient Search for Approved Drug Products, at http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm

2 - Maximum amount of this material in any dosage form recognized in the Database with a name beginning with "oral: capsule".

[redacted]

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/s/

RAYMOND P FRANKEWICH
09/17/2014

MOO JHONG RHEE
09/17/2014
Chief, Branch IV

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: August 15, 2014

FROM: Raymond P. Frankewich, Ph.D., Review Chemist, Branch IV, DNDQA II/ONDQA

THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, DNDQA II/ONDQA

TO: NDA 205718

SUBJECT: Final Recommendation

The previous CMC Review #1, dated 5-29-2014, made a recommendation of not approval of this NDA because of the following unresolved issues:

1. Final recommendation from the Office of Compliance has not been received.
2. Label/labeling issues were not satisfactorily resolved from the CMC perspective.

The Office of compliance has issued an overall "Acceptable" recommendation on **July 23, 2014** (**Attachment 1**).

Labels/labeling were revised according to our recommendations in CMC Review #1 (**Attachment 2**). Updated container labels were submitted on April 25, 2014 and July 16, 2014. Updated package insert was submitted on August 8, 2014.

In CMC Review #1 under II.C (Basis for Approvability or Not-Approval Recommendation), it is noted "(see the List of Deficiencies, p. 171)". This is a typographical error. The List of Deficiencies in CMC Review #1 begins on pg. 168.

Recommendation:

From the ONDQA perspective, this NDA is now recommended for **APPROVAL** with expiration dating period of 24 months.

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/s/

RAYMOND P FRANKEWICH
08/15/2014

MOO JHONG RHEE
08/15/2014
Chief, Branch IV

NDA 205718

Akynzeo® (netupitant and palonosetron) Capsules 300mg/0.5mg

Helsinn Healthcare SA

Raymond P. Frankewich, Ph.D.
Hitesh Shroff, Ph.D.
Nina Ni, Ph.D.

Review Team

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

CMC REVIEW
For the Division of Gastroenterology and Inborn Errors Products
(CDER/OND/ODEIII/DGIEP, HFD-180)

Table of Contents

CMC Review Data Sheet

1. NDA 205718

2. REVIEW #: 1

3. REVIEW DATE: 29-May - 2014

4. REVIEWERS: Raymond P. Frankewich, Ph.D.
Hitesh Shroff, Ph.D.
Nina Ni, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	September 27, 2013
Amendment	November 14, 2013
Amendment (labeling)	December 20, 2013
Amendment	February 5, 2014
Amendment	February 14, 2014
Amendment	March 27, 2014
Amendment	May 16, 2014
Amendment	May 27, 2014

7. NAME & ADDRESS OF APPLICANT:

Name: Helsinn Healthcare SA
Address: Via Pian Scairolo 9
Pazzallo – Lugano
Switzerland 6912

CMC Review Data Sheet

Representative: Dr. Craig Lehmann
August Consulting, Inc.
515 Capital of Texas Highway, Suite 150
Austin, Texas 78746
Telephone: 512-347-1755

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Akynzeo
b) Non-Proprietary Name (Per salt policy): Netupitant-palonosetron hydrochloride
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1, 4
- Submission Priority: S (under PDUFA V Program)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antiemetic (netupitant)
Antiemetic; antinauseant (palonosetron)

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 300 mg (netupitant)
0.5 mg (palonosetron)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

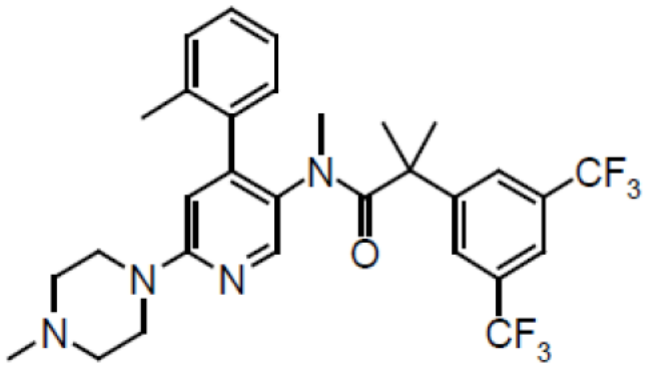
__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Netupitant

Chemical name (IUPAC name): 2-[3,5-bis(trifluoromethyl)phenyl]-N, 2-dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl] propanamide

Structural formula:

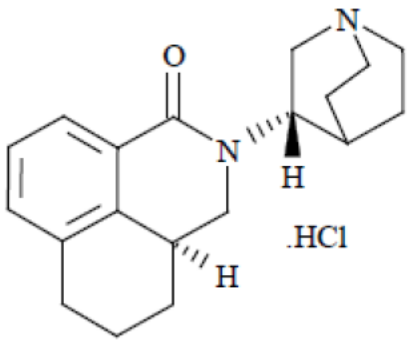


Molecular formula: $C_{30}H_{32}F_6N_4O$
Relative molecular mass: 578.61 g/mol

Palonosetron hydrochloride

Chemical name (IUPAC name): (3a*S*)-2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*]isoquinoline hydrochloride

Structural formula:



Molecular formula: $C_{19}H_{24}N_2O \bullet HCl$

Relative molecular mass: 332.87 g/mol

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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
26715	II	Helsinn Advanced Synthesis SA	Netupitant drug substance	1	Adequate	March 21, 2014	Reviewed by Hitesh Shroff
16063	II	Helsinn Advanced Synthesis SA	Palonosetron Hydrochloride	1	Adequate	February 27, 2014	Reviewed by Hitesh Shroff
(b) (4)	II		(b) (4)	1	Adequate	November 26, 2013	
	III			1	Adequate	October 29, 1997	Reviewed for oral (b) (4)
	III			1	Adequate	August 30, 2013	Reviewed for oral (b) (4)
	IV			1	Adequate	May 15, 2014	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-372	Aloxi® (palonosetron hydrochloride injection)
NDA	22-233	Aloxi® (palonosetron hydrochloride capsules)

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending	2/7/2014	
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Acceptable with modifications (see review)	4/29/2014	
DMETS	NA		
EA	Categorical exclusion (see review)		
Microbiology	NA		

The CMC Review for NDA 205718

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

However, a final "Acceptable" recommendation from Office of Compliance for the manufacturing facilities has ***not*** been made.

Also the information on the label/labeling currently is ***not*** acceptable from the CMC perspective.

Therefore, from the CMC perspective, this NDA is ***not*** ready for approval at this time in its present form per 21CFR314.125(b)(6),(13).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Throughout this review, the USAN name, palonosetron hydrochloride, is being used. However, per salt name policy, the established name will be presented as palonosetron. So when palonosetron is expressed for some reason, it actually represents palonosetron hydrochloride.

This drug product contains two drug substances, netupitant and palonosetron hydrochloride. Netupitant is a New Molecular Entity (NME). Both drug substances are antiemetics, and are intended to treat nausea and vomiting associated with chemotherapy.

Palonosetron hydrochloride and netupitant are designed to together treat acute nausea and vomiting (emesis) and delayed emesis.

Palonosetron hydrochloride is described as a well-known potent and selective 5-HT_3 receptor antagonist. Palonosetron hydrochloride has been marketed in the U. S. since 2003. An oral formulation of palonosetron hydrochloride (Aloxi® capsules 0.50 mg, NDA 22-233) was approved in 2008.

Netupitant is described as a novel, potent, and selective NK1 receptor antagonist.

Netupitant was discovered by Roche who performed early development studies on netupitant on its own. Roche subsequently licensed netupitant to this NDA applicant (Helsinn) who then developed the netupitant / palonosetron hydrochloride combination drug product.

Information from DMF 26715, held by Helsinn Advanced Synthesis SA, was reviewed for this NDA. Information from DMF 16063, also held by Helsinn Advanced Synthesis SA, was also reviewed for this NDA. Both reviews were performed by Hitesh Shroff, Ph.D.

(2) Drug Product

The drug product consists of a Size 0 hard gelatin capsule containing three 100 mg immediate-release tablets containing 100 mg netupitant, and one soft gelatin capsule (softgel) containing (b) (4) 0.50 mg of palonosetron (0.56 mg of palonosetron hydrochloride). Thus the dosage delivered by one capsule of the drug product is 300 mg netupitant and 0.5 mg palonosetron.

The design intent was to develop an oral fixed dose combination to allow administration of two drug substances in a single dosage form prior to each chemotherapy cycle.

The 100 mg netupitant tablet and the 0.50 mg palonosetron softgel are produced as intermediate drug products. They are referred to by the applicant as Intermediate Netupitant Tablet and Intermediate Palonosetron Softgel. The softgel is produced by (b) (4)

In this review, the Intermediate Netupitant Tablet is often referred to as INT, and the Intermediate Palonosetron Softgel is often referred to as (b) (4) The final combination capsule is referred to by the applicant as Netupitant Palonosetron

Combination Capsule. In this review, the combination capsule is often referred to as NPCC.

The proposed container closure system for the NPCC is a 1-unit blister package. The secondary package is an outer carton, containing the one-unit blister. Proposed shelf life for the NPCC is 24 months.

B. Description of How the Drug Product is Intended to be Used

According to the draft labeling, the adult dosage of the drug product is one capsule administered approximately one hour prior to the start of chemotherapy. The capsule can be taken with or without food.

C. Basis for Approvability or Not-Approval Recommendation

21 CFR 314.125(b)(13)

- No "Acceptable" recommendation from the Office of Compliance has been made for the cGMP compliance of the facilities involved.

21 CFR 314.125(b)(6)

- Labels and labeling issues have not been fully resolved

(see the **List of Deficiencies**, p. 171)

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Raymond P. Frankewich, Ph.D., Branch IV, ONDQA, DNDQA II.

B. Endorsement Block:

(See appended electronic signature page)

Moo Jhong Rhee, Ph.D., Branch Chief, Branch IV, ONDQA, DNDQA II

C. CC Block: entered electronically in DFS

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/s/

RAYMOND P FRANKEWICH
05/30/2014

MOO JHONG RHEE
05/30/2014
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Raymond P. Frankewich, CMC Reviewer

Office of New Drug Quality Assessment (ONDQA)
E-mail Address: raymond.frankewich@fda.hhs.gov
Phone: (301)-796-1354
Fax: (301)-796-9749

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3815

Through: John Kauffman, Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 205718

Name of Product: Akynzeo® (netupitant-palonosetron hydrochloride) capsule

Applicant: Helsinn Healthcare SA

Applicant's Contact Person: Dr. Craig Lehmann

Address: August Consulting, Inc.
515 Capital of Texas Highway, Suite 150
Austin, TX 78746

Telephone: (512) 347-1755 Fax: (512) 347-9375

Date Methods Validation Consult Request Form Received by DPA: 10/11/2013

Date Methods Validation Package Received by DPA: 10/11/2013

Date Samples Received by DPA: 11/18/2013

Date Analytical Completed by DPA: 4/28/2014

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☐
2. Methods are acceptable with modifications (as stated in accompanying report). ☒
3. Methods are unacceptable for regulatory purposes. ☐

Comments: Analyst's comments and link to analyst's work sheets are attached.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis, Missouri 63110
Telephone (314) 539-3858
FAX (314) 539-2113

Date: April 25, 2014

To: Raymond P. Frankewich, Ph. D., CMC Reviewer, ONDQA
Marie Kowblansky, Ph. D., CMC Lead, ONDQA

Through: John Kauffman, Ph. D., Deputy Director, Division of Pharmaceutical Analysis

From: Anjanette Smith, Chemist, Division of Pharmaceutical Analysis

Subject: Method Validation for NDA 205718
Akynzeo ® (netupitant-palonosetron hydrochloride) Capsule
Helsinn Healthcare SA

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

- Related Substances and Identification by HPLC, drug substance (ALC/146)
- Assay by HPLC, drug substance (ALC/147)
- Netupitant Impurities, drug product (32P25-7)
- Assay of Netupitant, drug product (32P52-5)
- Dissolution - Netupitant, drug product (32P52-11)

The following method was evaluated and is acceptable for quality control and regulatory purposes with modification:

- (b) (4) - Netupitant, drug substance (AGC/166)

(b) (4)

Analyst's work sheets and data are available at http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f88068cb0c

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/s/

MICHAEL L TREHY
04/28/2014

JOHN F KAUFFMAN
04/29/2014