

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206500Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:

This 505(b)(1) NME application is **not** deemed ready for **Approval** as of this review in its present form, per 314.125(b)(6).

NDA 206500

Review #1

Review Date: May 1, 2015

Drug Name/Dosage Form	VARUBI (rolapitant) tablets
Strength	90 mg (equivalent to 100mg of rolapitant hydrochloride)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Tesaro, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	9/5/2014
Amendment	12/5/14
Amendment	12/22/14
Amendment	3/26/15
Amendment	4/2/15
Amendment	4/22/15

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Charles Jewell, Ph.D.	OPQ/ONDP/NDAP/Branch 1
Drug Product	Hitesh Shroff, Ph.D.	OPQ/ONDP/NDPII/Branch V
Process	Akm Khairuzzaman, Ph.D.	OPQ/OPF/DIV-1/BRANCH-1
Microbiology	Bryan Riley, Ph.D.	OPQ/OPF/DMA/BII
Facility	Christina Capacci-Daniel, Ph.D.	OPQ/OPF/DIA/IABII
Biopharmaceutics	Peng Duan, Ph.D.	OPQ/ONDP/DB/Branch II
Project/Business Process Manager	Olga Simakova, Ph.D.	OPRO/Div I/ Branch-I
Application Technical Lead	Moo-Jhong Rhee, Ph.D.	OPQ/ONDP/NDPII/Branch V
Laboratory (OTR)	na	
ORA Lead	Sharon Thoma, Pharm.D.	ORA/OMPTO/MIN-DO
Environmental Assessment (EA)	James Laurenson, Ph.D.	OPQ/ONDP

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Quality Review Data Sheet

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

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
N/A	Type II					
(b) (4)	Type III (if applicable)		(b) (4)	N/A	Dec 29, 2014	Adequate, Elise T Luong, Ph.D.
	Type III			N/A	Apr 29, 2014	Adequate, Edwin Jao, Ph.D.
	Type III			N/A	Sept 26, 2014	Adequate, Ping Jiang-Baucom, Ph.D.
N/A	Type IV (if applicable)					
	Other					

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	072754	

3. CONSULTS: N/A

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

The office of Compliance has made a final “Acceptable” recommendation for the facilities involved in this application.

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

However, the labels/labeling issues have *not* been completely resolved as of this review.

Therefore, from the ONDP perspective, this NDA is *not* deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6), until the above issues are satisfactorily resolved (see the **List of Deficiencies** on p. 133).

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

N/A

II. Summary of Quality Assessments

The proposed drug, VARUBI (rolapitant) 90mg tablets, is an antiemetic drug for the prevention of (b) (4) delayed nausea and vomiting (b) (4) emetogenic cancer chemotherapy. The drug product contains an active ingredient, rolapitant hydrochloride, which acts *in vivo* as an NK1 receptor antagonist. It is classified as an NME.

The phase 1 and 2 clinical trials were conducted with two clinical batches of 50mg (rolapitant hydrochloride) capsules, and an optimum dose was determined to be 200mg (4x50mg capsules). (b) (4)

(b) (4) After extensive pharmaceutical developmental studies, 100mg film coated tablets are proposed for this application as a to-be-marketed product. The dose for the treatment is 2x100mg tablets, which are deemed bioequivalent to 4x50mg capsules.

To be in line with USP salt policy for the active ingredients, the strength is changed from 100mg (rolapitant hydrochloride) to 90mg (rolapitant).

A. Drug Substance (rolapitant hydrochloride) Quality Summary

Rolapitant hydrochloride,

(5S,8S)-8-[[[(1R)-1-[3,5 Bis(trifluoromethyl)phenyl]ethoxy]methyl]-8-phenyl-1,7-diazaspiro[4.5]decan-2-one hydrochloride monohydrate,

is a white to off-white powder.

(b) (4)

(b) (4)

(b) (4)

The control strategy for the proposed starting material was discussed at the EOP-2 meeting (Jan-28-2013) including its specification, and it was deemed acceptable

(b) (4)

(b) (4)

(b) (4)

(b) (4) month of retest period is proposed, and granted.

(b) (4)

B. Drug Product [rolapitant hydrochloride] Quality Summary

For phase 1 and 2 clinical trials, 50mg capsules were developed, and for the pivotal clinical trials, a dose of 200mg (4x50mg capsules) was selected and found

to be safe and efficacious.

(b) (4)

After further developmental studies, 100mg film coated tablets were proposed as the commercial product, which were demonstrated to be bioequivalent to 50mg capsules (2x100mg tablets vs 4x50mg capsules).

Each tablet contains 100mg of rolapitant hydrochloride and excipients; lactose monohydrate, pregelatinized starch, microcrystalline cellulose, povidone (b) (4), croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, (b) (4) blue, and (b) (4) clear, with a total weight of 520mg.

The lactose monohydrate is derived from bovine source, and the applicant states that it complies with all Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE) applicable US and EU regulations. A certificate of analysis to that effect was submitted and deemed satisfactory.

The proposed strength for the tablet was changed from 100mg (rolapitant hydrochloride) to 90mg (rolapitant) to be in line with USP salt policy, which precludes the salt from the established name.

ID tests are based on UV and HPLC; strength ((b) (4) %) is assured with assay and content uniformity; total related substances are controlled less than (b) (4) % with individual being less than (b) (4) %; and dissolution is set at (b) (4) % in 30 min

Two 90mg tablets are packaged in an ACLAR/foil twin-blister as a single dose for 180mg.

Based on the stability data submitted, 24-month of expiration dating period was proposed and deemed well justified.

C. Manufacturing Process

(b) (4)

D. Biopharmaceutics

The applicant has demonstrated bioequivalence through the study PR-1054-C between 50mg (rolapitant hydrochloride) capsules and 100mg (rolapitant hydrochloride) tablets.

The proposed dissolution test and acceptance criterion, (b) (4) % at 30 minutes is considered to be satisfactory.

E. Facilities (see the Attachment 1)**F. Environmental Assessment**

The applicant claimed for the exclusion from the Environmental Assessment, and is granted.

G. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	VARUBI
Non Proprietary Name of the Drug Substance	Rolapitant hydrochloride
Proposed Indication(s) including Intended Patient Population	Nausea and vomiting for emetogenic cancer chemotherapy
Duration of Treatment	During each cancer chemotherapy cycle
Maximum Dose	200mg for each cancer chemotherapy cycle
Alternative Methods of Administration	N/A

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

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Moojhong Rhee -S,
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Date: 2015.05.04 10:16:06 -04'00'

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

Applicant's Response:

Structure, Naming, Pharmacology Related Info:

- USAN: Rolapitant Hydrochloride
- INN: (5S,8S)-8-[[[(1R)-1-[3,5 Bis(trifluoromethyl)phenyl]ethoxy]-methyl]-8-phenyl-1,7-diazaspiro[4.5]decan-2-one
- **Chemical Name:** (5S,8S)-8-[[[(1R)-1-[3,5 Bis(trifluoromethyl)phenyl]ethoxy]-methyl]-8-phenyl-1,7-diazaspiro[4.5]decan-2-one hydrochloride monohydrate
- CAS: 552292-08-7 (as free base); 914462-92-3 (as hydrochloride monohydrate)
- Codes: SCH 619734 hydrochloride monohydrate; (b) (4) Rolapitant

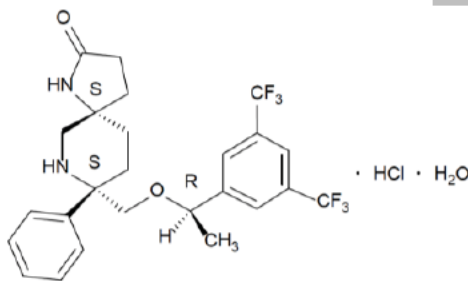


Figure 1: Rolapitant hydrochloride monohydrate

Chemical Formula: $C_{25}H_{29}ClF_6N_2O_3$ or
 $C_{25}H_{26}F_6N_2O_2 \cdot HCl \cdot H_2O$

(b) (4)

Molecular Weight: 554.95
S,S,R Configuration

- This molecule has been determined to be a substance P, neurokinin 1 (NK1) receptor antagonist. It is indicated for use in combination with other anti-emetic agents for prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of (b) (4) emetogenic cancer chemotherapy. The proposal is to give one 200 mg dose prior to each round of chemotherapy.

Physical Properties and Related Functional Properties:

- Rolapitant hydrochloride monohydrate appears as white to off-white powder.

(b) (4)

Biopharmaceutical Class System Related Information:

- Rolapitant is completely bioavailable in humans when orally administered in the fasted state (5mg to 200 mg). It is rapidly absorbed. It is slowly metabolized and eliminated. It reaches a plasma concentration of 1000 ng/mL (C max). The mean terminal half-life is 169 to 183 hours. The volume of distribution is high (~460 L). It is highly bound to plasma proteins. It is readily metabolized by oxidation to SCH 720881, which demonstrates nearly equal inhibitory potency against NK1. The major route of elimination is via the feces/biliary pathway. Only 14% of elimination is renal.
- Caco-2 cells studies indicate high permeability with no significant efflux. Absorption in humans is not expected to be permeability limited.
- It's low solubility coupled with high permeability would render it a BCS class II molecule.
- The NK1 receptors is a G-protein coupled receptor. It has seven hydrophobic transmembrane spanning domains. It links activities outside of cell to activities within the cell. Significant cell penetration of this compound is not necessary for activity.

Reviewer's Assessment: There is adequate understanding of the drug substance physical, chemical, biological and mechanical aspects to support the use of this drug substance in further processing. The process reviewer expressed concern over

(b) (4)

(b) (4)

Based on data in the application demonstrating high human bioavailability of the compound and long biological half-life, the risks of dramatically altering the availability of this substance to the patient due to potential

(b) (4)

The sponsor responded to the process reviewer's IR on 12/22/2014. They provided further data demonstrating the

(b) (4)

2.3.S.2 Manufacture***S.2.2 Description of the Manufacturing Process and Controls***

1. Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug substance batches? (Note: add applicant's response and reviewers assessment box after this question)

Applicant's Response:

(b) (4)

ppm). No detectable levels have been found in batches of 619734-GB (11 lots). It was adequately demonstrated that the [REDACTED] (b) (4)

- Adequate specification for all solvents, reagents and other materials were presented in the application.

Reviewer's Assessment: The process is adequately described. Starting material designation is adequately justified, with the strategy for assessing the input starting material criteria, and adequate specifications provided. Critical quality attributes are reasonably determined and justified. The attributes are adequately controlled by the appropriate selection of in-process-controls. Operating parameters were investigated to ensure appropriate robustness for the process, and the normal operating ranges for the critical parameters are well within the acceptable ranges. At all steps, materials are controlled and re-worked if necessary to achieve an adequate quality of drug substance by this process.

2. Is there any proposal for online/at line/in line monitoring technologies for routine commercial production that allows for real-time process monitoring and control? If so, is it acceptable?

Applicant's Response:

[REDACTED] (b) (4)

Reviewer's Assessment:

[REDACTED] (b) (4)

Control of Critical Steps and Intermediates

3. What are the critical steps which could significantly affect the structure of the drug substance and impurity profiles? If so, are the critical process parameters (CPPs) adequate to ensure the identity and purity of the drug substance?
4. Are intermediates controlled adequately to assure the structure and impurity profile of the final drug substance?

Applicant's Response:

[REDACTED] (b) (4)

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition of the Drug Product

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Rolapitant tablets are 90 mg immediate release film-coated capsule shaped blue tablets, debossed with T0101 on one side and 100 on the other side. Each tablet contains 90 mg rolapitant equivalent to 100 mg rolapitant hydrochloride. The drug product is packaged in ACLAR®/foil twinned blister containing two 90 mg tablets. (b) (4)

The qualitative and quantitative composition of the drug product is shown in the table below.

*In the review, 90mg rolapitant tablets and 100mg rolapitant hydrochloride tablets are interchangeably used, when it is appropriate.

Composition of Rolapitant tablets

Component	Quality Grade	Function	Unit Formula (mg/unit)
(b) (4)			
Drug Substance (b) (4)	Internal specifications	(b) (4)	
Lactose Monohydrate	USP/NF, Ph Eur	(b) (4)	
Pregelatinized Starch	USP/NF, Ph Eur		
Microcrystalline Cellulose (b) (4)	USP/NF, Ph Eur		
Povidone (b) (4)	USP, Ph Eur		
Croscarmellose Sodium	USP/NF, Ph Eur		
(b) (4)			
Microcrystalline Cellulose (b) (4)	USP/NF, Ph Eur	(b) (4)	
Croscarmellose Sodium	USP/NF, Ph Eur	(b) (4)	
Colloidal silicon dioxide	USP/NF, Ph Eur		
Magnesium Stearate	USP/NF, Ph Eur		
Film Coating			
(b) (4) Blue	USP/NF, Ph Eur ^d	(b) (4)	
(b) (4) Clear	USP/NF, Ph Eur	(b) (4)	
Total Tablet Weight			520.0

The excipients of (b) (4) Blue and (b) (4) Clear are shown in the tablet below.

List of excipients in (b) (4)

Coating Material	Components
(b) (4) Blue	Polyvinyl Alcohol (USP/NF, Ph. Eur.) (b) (4) (USP/NF, Ph. Eur.) Polyethylene Glycol (USP/NF, Ph. Eur.) Talc (USP/NF, Ph. Eur.) FD&C Blue #2/Indigo Carmine Lake (complies with CFR title 21 part 74.102 and EC directive 2008/128/EC)
(b) (4) Clear	Polyvinyl Alcohol, (b) (4) (USP/NF, Ph. Eur.) Talc (USP/NF, Ph. Eur.) Polyethylene Glycol (USP/NF, Ph. Eur.) (b) (4) (USP/NF, Ph. Eur.)

Reviewer's Assessment:

The applicant has provided the quantitative and qualitative compositions of the drug product. The table also includes the function and amount of each excipient. All ingredients in the drug product are compendial grades. The API is controlled by internal specification (Sec. 3.2.P.3.1). There are no novel excipients. The tablets are packaged in ACLAR/foil blister (b) (4)

The tablets contain bovine derived lactose monohydrate as one of the excipients, and the applicant states that it complies with all Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE) applicable US and EU regulations. A certificate of analysis to that effect was submitted.

Conclusion: Adequate

The applicant has provided sufficient information including the quality, functions and amounts of all ingredients used in the drug product formulation

2.3.P.2 Pharmaceutical Development

17. *Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?*

The primary goal of the formulation development was to provide an oral immediate release film coated rolapitant tablet which is stable during the entire shelf life, meets specification, and can be produced by a robust scalable manufacturing process.

The following is a list of 2.5 mg, 10 mg and 50 mg (b) (4) formulations used in initial clinical studies. (b) (4)

Composition of initial (b) (4) formulations

Component	2.5 mg		10 mg		50 mg	
	[mg]	[wt% fill]	[mg]	[wt% fill]	[mg]	[wt% fill]
Drug Substance	(b) (4)					
Lactose Monohydrate						
Pregelatinized Starch						
Croscarmellose Sodium						
(b) (4)						
Microcrystalline Cellulose						
(b) (4)						
Croscarmellose Sodium						
Magnesium Stearate						
(b) (4)						
(b) (4) blue						
(b) (4)						
Total fill	(b) (4)					

Subsequently 100 mg rolapitant hydrochloride tablet formulation was developed under the sponsorship of Schering Plough. The bioavailability of 100 mg rolapitant hydrochloride tablet formulation was found to be comparable to 50 mg capsules (BA Study P04854).

Additionally the bioavailability (Study PR-10-5000-C) of (b) (4) rolapitant hydrochloride tablet and (b) (4) rolapitant hydrochloride capsule formulation demonstrated low bioavailability compared to 50 mg rolapitant hydrochloride capsule formulation.

In order to determine the effects of formulation and dissolution on the bioavailability, a number of parameters (b) (4)

evaluated.

Based on the favorable results from the bioavailability study (PR-10-5007-C) together with dissolution and manufacturability as well as long-term and accelerated stability data, 90 mg rolapitant (equivalent to 100 mg rolapitant hydrochloride) tablet was selected for commercial formulation (see tables below).

Summary of results of parameters tested using 90 mg rolapitant tablet

Parameter	Result
(b) (4)	

Composition of formulation for clinical BA and BE studies

Formulation	50 mg capsule		100 mg tablet (Schering)		(b) (4)		100 mg tablet (b) (4)		100 mg tablet (b) (4)		100 mg tablet (commercial)	
Composition	[mg]	[wt%]	[mg]	[wt%]	[mg]	[wt%]	[mg]	[wt%]	[mg]	[wt%]	[mg]	[wt%]
(b) (4) Drug Substance	(b) (4)											
Lactose Monohydrate	(b) (4)											
Pregelatinized Starch	(b) (4)											
Microcrystalline Cellulose (b) (4)	(b) (4)											
Povidone (b) (4)	(b) (4)											
Croscarmellose Sodium (b) (4)	(b) (4)											
Microcrystalline Cellulose (b) (4)	(b) (4)											
Croscarmellose Sodium	(b) (4)											
Colloidal silicon dioxide	(b) (4)											
Magnesium Stearate (b) (4)	(b) (4)											
(b) (4) Blue	(b) (4)											
(b) (4)	(b) (4)											
(b) (4) Clear	(b) (4)											
Total core/fill	(b) (4)											
BA/BE Evaluation ^d	Study number	Phase I/II/III	P04854	PR-10-5000-C		PR-10-5007-C		PR-10-5013-C PR-10-5014-C		PR-10-5014-C		
	Results/comments (BE reference is 50 mg capsule)	N/A	comparable (but slightly lower) BA (b) (4)	Low BA	Low BA	BE criteria met	BE criteria met	BE criteria met in PR-10-5014-C				

For the commercial scale production of the 100 mg rolapitant hydrochloride tablets under cGMP conditions, (b) (4)

The following is a summary of batches produced (b) (4)

using the proposed manufacturing process and specification.

(b) (4)

Uniformity of dosage units: It was determined by the (b) (4)
(b) (4) CTMLP-3019, used for assay and impurities. It is summarized in Sec. 3.2.P.5.2.2.4. The acceptance value is calculated per USP<905>.

(b) (4)

Microbial enumeration: The microbial count, total yeast and mold count and the test for E. Coli are determined per USP <61> and USP <62> respectively.

Validation of Analytical Methods:

The analytical methods for identification, assay and impurities, content uniformity, (b) (4) and dissolution were validated at (b) (4)

The following is a summary of tests, analytical methods and validation reports provided in Sec. 3.2.P.5.3.

Validation reports for rolapitant tablets

Test	Method	Validation Report
Description	Visual	N/A
Identification – UV Spectrum	CTMLP-3019	TES-AR-039-0614-R0
Identification - HPLC		TES-AR-021-0813-R0 (Part A) TES-AR-039-0614-R0 TES-AR-040-0614-R0
Assay		
Individual Related Impurities/Degradation Products		
Total Related Impurities/Degradation Products		
Uniformity of Dosage Units		TES-AR-021-0813-R0 (Part A)
Dissolution	CTMLP-3185	TES-AR-018-0613-Ro (Part A)
(b) (4)	CTMLP-3024	TES-AR-017-0613-R0
Microbial Enumeration	USP <61 and <62>	MM-1513

Identification by UV spectroscopy and HPLC: This method is validated for selectivity by UV and HPLC retention time of the sample and reference standard.

Assay, impurities and dosage uniformity: The HPLC method, CTMLP-3019, was validated for specificity, linearity and range, accuracy, intermediate precision, limit of detection and quantitation, robustness, reference standard and sample stability. The validation parameters, acceptance criteria and results are provided in a tabular format in Sec. 3.2.P.5.3.2.4. Based on the results of the method validation, it was concluded that the HPLC method, CTMLP-3019, is suitable for the tests of assay and impurities and dosage uniformity. This is deemed to be the stability indicating method.

(b) (4)

The

results of the method validation were submitted in a tabular format in Sec. 3.2.P.3.2.6.

The working standard and sample solutions were determined to be stable for up to 13 days at room temperature and also under refrigeration (2°C to 8°C).

Reviewer's Assessment:

The analytical methods used to determine assay, impurities, dosage uniformity, dissolution, (b) (4) and microbial enumeration of the drug product are deemed adequate to assure identity, strength, purity and quality of the drug product. The analytical methods outlined in Sec. 3.2.P.5.3 are in accordance with ICH Guideline Q2(R1). These methods are validated for linearity, specificity, precision, accuracy, detection and quantification limits (LoD and LoQ) and solution stability. No interfering peaks were observed in any of the methods. Each method is specific to the drug product, related substances or excipients and it suitable for its intended use. The HPLC method for assay and impurities, CTMLP-3019, was deemed acceptable by FDA, Division of Pharmaceutical Analysis, St. Louis, MO. The following is a summary of the methods validation report from FDA, DPA.

Methods validation report summary:

SUBJECT: Methods Validation Report Summary

Application Number: 206500

Name of Product: (b) (4) (Rolapitant) tablets, 100 mg

Applicant: Tesaro, Inc.

Applicant's Contact Person: Gabriela Rossi, Director, Regulatory Affairs

Address: 1000 Winter Street North, Suite 300, Waltham, MA 02451

Telephone: (781) 810-4772 Fax: (339) 230-3976

Date Methods Validation Consult Request Form Received by DPA: November 10, 2014

Date Methods Validation Package Received by DPA: November 10, 2014

Date Samples Received by DPA: November 26, 2014

Date Analytical Completed by DPA: February 26, 2015

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: See attached summary for analyst comments and results.

Table 2. Specification for Rolapitant, 100 mg tablets

	Criteria	Observation	Pass/Fail
Identification	(b) (4)	(b) (4)	PASS
Assay	(b) (4) of the Label Claim	(b) (4)	PASS
Impurities/Degradation Products	Individual: NMT (b) (4)	(b) (4)	PASS
	Total: NMT (b) (4)	Total (b) (4)	PASS

Conclusion: Adequate

All analytical methods are appropriately described and validated for their intended use and deemed adequate for assuring the quality of the drug product at release and for storage during shelf-life. In addition, the HPLC method for assay and impurities was deemed acceptable after validation by FDA, Division of Pharmaceutical Analysis, St. Louis, MO.

2.3.P.7 Container Closure System

6. Is the proposed container closure system (describe it briefly with diagrams, if available) adequate to protect the product from the environment (oxygen, moisture) to ensure the strength, purity (extractables/leachables), and performance of the drug product through the proposed expiration dating period?

The Rolapitant tablets are supplied in ACLAR®/foil blister strips. Each blister contains two 90 mg rolapitant tablets. The to-be marketed product will be

(b) (4)
a single dose (b) (4) containing two
tablets in a single blister. (b) (4)

The The blister is composed of (b) (4)
polychlorotrifluoroethylene (ACLAR®). The aluminum foil

(b) (4)

The applicant has provided the description, name of the manufacturers, product codes, materials of construction, dimensions, specifications, part numbers, DMF references with LoAs and CoAs of ACLAR® (b) (4) from the suppliers. Both CoAs stated that the materials are in compliance with applicable 21 CFR 174-186 sections for indirect food additive regulations.

The DMF (b) (4) was last reviewed on April 29, 2014 and DMF (b) (4) was last reviewed on September 26, 2014. Both DMFs were deemed adequate.

The compatibility and suitability of the container closure system was demonstrated by the stability of drug product packaged in ACLAR® blisters at 40°C/75%RH up to 6 months and 50°C/ambient RH up to 2 months. The appearance, assay, dissolution and related impurities were within the acceptance limits during the stability testing period.

Specification for ACLAR® film

Test	Acceptance Criterion
Description	(b) (4) Aclar® (b) (4)
Dimensions - Width - Roll O.D. - Core I.D.	(b) (4)
Materials - Construction - Color - Thickness - Yield	- Aclar® (b) (4) (b) (4) - Clear (b) (4) (b) (4) (b) (4)
Packing and Marking (b) (4)	(b) (4) (b) (4)

Specification for Aluminum foil

Test	Acceptance Criterion
Description	Aluminum Foil, 20 µm, Blister Lidding, Push-Through, 160mm (b) (4)
Dimensions - Width - Roll O.D. - Core I.D.	(b) (4)
Materials - Construction - Basis Weight	(b) (4) (b) (4)
Packing and Marking (b) (4)	(b) (4) (b) (4)

Referred to as (b) (4) in sections 3.2.P.8.1 and 3.2.P.8.3

Reviewer's Assessment:

The applicant has adequately demonstrated that the container closure is appropriate to (b) (4). The safety of the materials of construction of the container closure is supported by the CoAs and reference to

appropriate indirect food additive regulations 21 CFR 174-186 sections. The suitability and compatibility is demonstrated by the stability studies of the drug product in blisters. For the quality control of ACLAR® film and aluminum foil the applicant has provided specifications and referenced the DMFs.

The applicant has provided adequate information to demonstrate that the container closure system is adequate to insure drug product integrity and performance through the intended shelf life.

Conclusion: Adequate

The applicant has provided sufficient information to establish that the container closure system is adequate (b) (4) during the expiration dating period.

2.3.P.6 Reference Standards or Materials

7. Are the proposed drug product reference standards acceptable?

The rolapitant hydrochloride monohydrate standard used for the drug product analysis is SCH 619734. It was also used for the analysis of the drug substance. The same impurities reference standards for drug substance were also used in the drug product method validation and system suitability methods. There are no specified impurities related to the drug product manufacturing or leachables from the container closure. The reference standards are described in detail in Sec. 3.2.S.5.

Reviewer's Assessment:

The applicant has provided adequate information on the reference standards including characterization and CoAs.

Conclusion: Adequate

2.3.P.8 Stability

8. What is the proposed shelf-life for the drug product? Do the product stability studies and data support the proposed shelf life and storage conditions in the commercial container/closure system? Does the statistical evaluation of the stability data and observed trends support the proposed shelf-life? Are the post-approval stability protocols and other stability commitments for the drug product adequate?

The long-term stability study up to 12 months and accelerated up to 6 months stability study of three registration batches (b) (4) This was agreed at the EOP 2 meeting on 2/8/13) packaged in the to-be marketed blister made of Film (Aclar® (b) (4)) with a backing

aluminum foil (b) (4). These batches were made using the drug substance (Batch (b) (4)) from the manufacturer, (b) (4). Both drug substance and drug product were manufactured using the proposed commercial manufacturing processes at (b) (4). The stability studies were performed in accordance with ICH Q1A (R2) guidance. During the stability studies, at each time point, description, (b) (4) assay, dissolution and impurities were assessed. The microbial testing was performed at time-0 and 12-month only during the long-term stability testing. From the stability data, it was concluded that there was no significant change in the strength, purity and quality of the drug product up to the period tested.

Based on these results, the applicant proposed 24-month expiration dating period when stored at (b) (4) C. The long-term and accelerated stability study results were provided in a tabular format in Sec. 3.2.P.8.3.

The tablets (b) (4) to-be-marketed drug product will be debossed without any ink. (b) (4)

The to-be-marketed tablets will be coated with blue and clear coatings (b) (4) blue and Clear). The applicant has provided (b) (4) study on one batch of drug product (b) (4)

The photostability testing on one batch of tablets unpackaged and packaged in blisters was conducted for (b) (4). There was no significant change observed in the description, (b) (4) assay, dissolution and impurities between the control and the samples. A summary of the results were submitted in Sec. 3.2.P.8.1.3.2.

The freeze-thaw study of the tablets packaged in blisters was conducted over a two week period (7-day cycle between -20°C and 50°C). During the photostability and freeze-thaw cycles stability studies description, (b) (4) assay, dissolution and impurities were assessed. A summary of the results were submitted in Sec. 3.2.P.1.3.4.

Primary stability batches of rolapitant tablets, 90 mg

Manuf. Site	Batch Number	Batch Size (Units)	Mfd	Use	Months Available	Storage Condition	Package Type	Drug Substance
(b) (4)	MPVW ¹ , KXVY ²	(b) (4)	(b) (4)	Registration, stability, clinical	12	25°C/60%RH	(b) (4)	(b) (4)
						30°C/65%RH ³		
						40°C/75%RH		
	MPVX ¹ , KXVZ ²			Registration, stability	12	25°C/60%RH		
						30°C/65%RH ³		
						40°C/75%RH		
	MPVX ¹ , KXVZ ²			Photostability, Freeze-thaw	NA	(b) (4)		
	MPVY ¹ , KXWB ²			Registration, stability	12	25°C/60%RH 30°C/65%RH ³ 40°C/75%RH		
	KKXB ^{1,2}			Technology transfer, supportive stability	12	25°C/60%RH 30°C/65%RH ³ 40°C/75%RH		
	KXVY			(b) (4) stability	12	20°-25°C (Controlled Room Temperature)		
(b) (4)								

Rolapitant tablets, 90 mg registration batches registration batches stability studies

Storage Condition	Description
25°C/60% RH	25 ± 2°C/60% ± 5% RH (long-term storage)
30°C/65% RH	30 ± 2°C/65% ± 5% RH (intermediate condition)
40°C/75% RH	40 ± 2°C/75% ± 5% RH (accelerated storage)
(b) (4)	20–25°C (Controlled Room Temperature [CRT])
Photostability	Ambient Storage (b) (4)
Freeze-Thaw	

The stability studies of the registration batches are on going as summarized in the table below. The applicant committed to withdraw from the market any out-of-spec lots per 3.2.P.5.1, and if it is a single occurrence then it will be discussed immediately with the agency according to 21 CFR 314.81(b)(1)(ii).

Stability protocol for registration batches of Rolapitant tables, 90 mg

Test name (method)	Storage condition	Time (months)							
		1	3	6	9	12	18	24	36
Appearance	25°C/60% RH		x	x	x	x	x	x	x
	30°C/65% RH	y	y	y	y	y			
	40°C/75% RH	x	x	x					
(b) (4)	25°C/60% RH		x	x	x	x	x	x	x
	30°C/65% RH	y	y	y	y	y			
	40°C/75% RH	x	x	x					
Potency Assay	25°C/60% RH		x	x	x	x	x	x	x
	30°C/65% RH	y	y	y	y	y			
	40°C/75% RH	x	x	x					
Dissolution (profile)	25°C/60% RH		x	x	x	x	x	x	x
	30°C/65% RH	y	y	y	y	y			
	40°C/75% RH	x	x	x					
Related substances	25°C/60% RH		x	x	x	x	x	x	x
	30°C/65% RH	y	y	y	y	y			
	40°C/75% RH	x	x	x					
Microbial limits test	25°C/60% RH					x		x	x

x = pull and test sample

y = pull and test sample only if 40°C/75% RH sample fails specification or exhibits significant changes

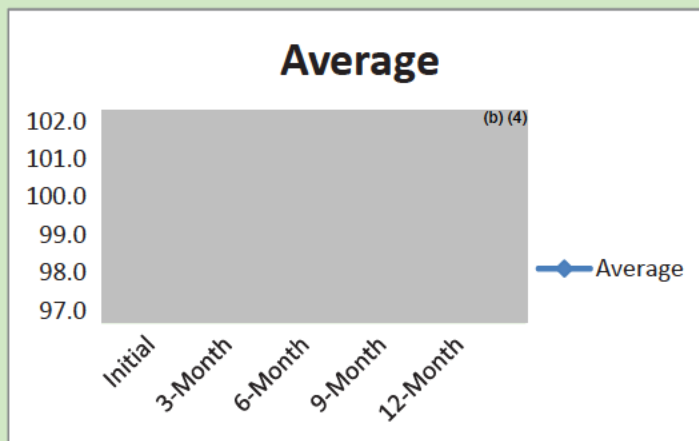
The applicant also provided stability protocol for first three commercial batches of the drug product and stability protocol for post-validation commercial batches of the drug product. During the long-term and accelerated stability studies, appearance, (b) (4) assay, dissolution, impurities and microbial purity will be assessed.

Reviewer's Assessment:

The applicant has performed 12-month long-term, 6-month accelerated stability studies, including the effect of light, freeze-thaw on the product. Stability of the bulk drug product during storage before packaging was also studied. All the studies were conducted per ICH Q1(A)(R2) guidance.

The applicant has provided a list of stability batches tested, storage conditions used, product attributes tested, shelf-life acceptance criteria, test schedule and stability data. From the stability data, it appears that there was no significant change in the description, (b) (4) drug substance assay, impurities, dissolution and microbial purity during the course of the stability studies.

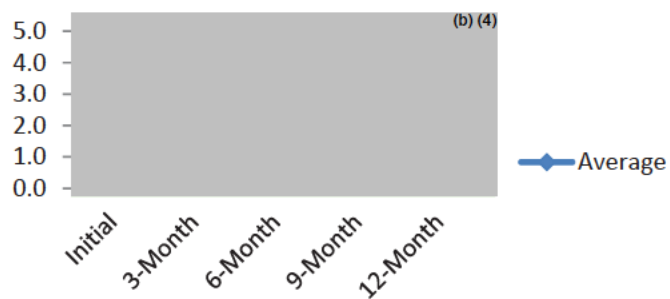
As shown in the following plot of average results of each time period during the long-term and accelerated stability testing, it is evident that all three batches met the specification for assay, dissolution and (b) (4). The individual impurity and total impurities were within the acceptance limits (NMT (b) (4) % and NMT (b) (4) % respectively) during the entire stability testing period.

Stability at 25°C/60% RH**Assay**

Stability at 25°C/ 60% RH - Assay					
Batches	Initial	3-Month	6-Month	9-Month	12-Month
MPVW	(b) (4)				
MPVX					
MPVY					
Average					

(b) (4)

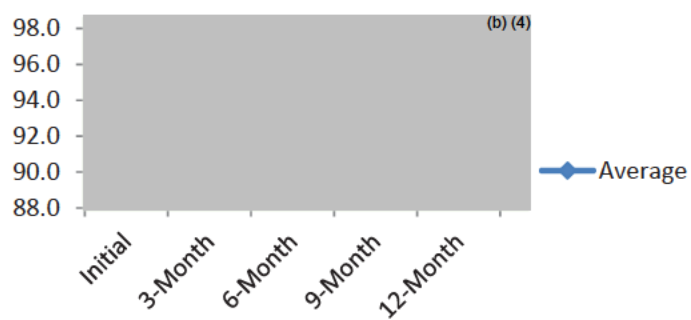
Average



Stability at 25°C/ 60% RH					
Batches	Initial	3-Month	6-Month	9-Month	12-Month
MPVW	(b) (4)				
MPVX					
MPVY					
Average					

Dissolution

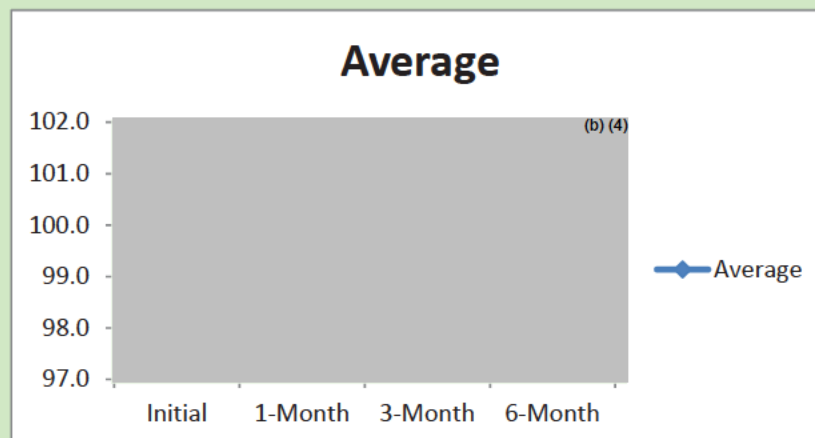
Average



Stability at 25°C/ 60% RH - Dissolution					
Batches	Initial	3-Month	6-Month	9-Month	12-Month
MPVW	(b) (4)				
MPVX					
MPVY					
Average					

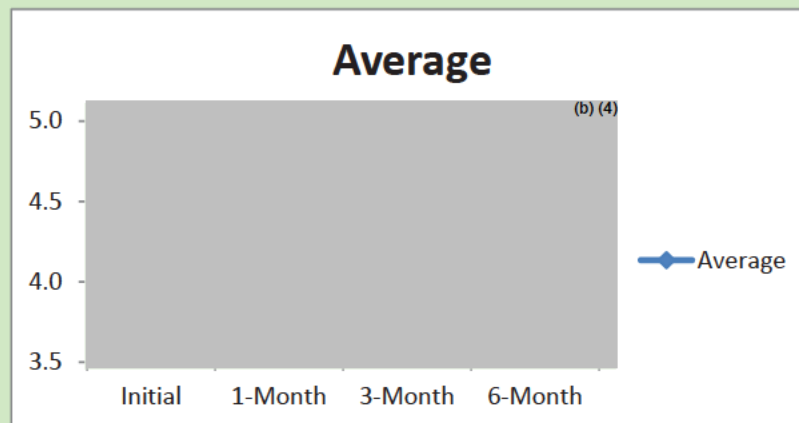
Stability at 40°C/75% RH

Assay



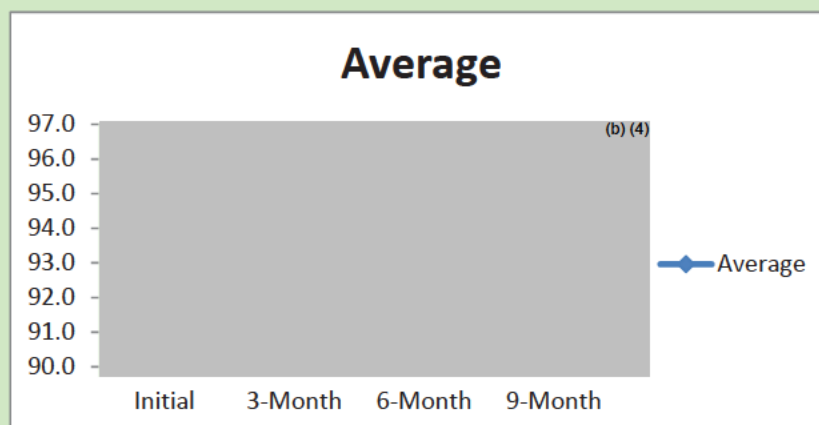
Stability at 40°C/ 60% RH - Assay				
Batches	Initial	1-Month	3-Month	6-Month
MPVW	(b) (4)			
MPVX				
MPVY				
Average				

(b) (4)



Stability at 40°C/ 60% RH - (b) (4)				
Batches	Initial	1-Month	3-Month	6-Month
MPVW	(b) (4)			
MPVX				
MPVY				
Average				

Dissolution



Stability at 40°C/ 60% RH - Dissolution				
Batches	Initial	3-Month	6-Month	9-Month
MPVW	(b) (4)			
MPVX				
MPVY				
Average				

The applicant has provided adequate post approval stability testing protocol and stability testing commitment.

The stability testing conditions and the length of studies are sufficient for storage, shipment and subsequent use.

Based on the stability data provided, the proposed 24-month expiration dating period for the drug product is acceptable.

Conclusion: Adequate

The applicant has performed stability studies with three registration batches per ICH Q1(A)(R2) guideline, and demonstrated that the rolapitant tablets are deemed to maintain the physical and chemical characteristics, which are comparable to the clinical batches used in the pivotal clinical trials, and expected to provide the same safety and efficacy benefit to patients during the expiration dating period.

R.2 Comparability Protocols

9. *Is a Comparability Protocol included in the application for post approval changes that might affect drug product quality including sterility assurance? If so, what post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?*

The applicant did not propose any comparability protocols.

Reviewer's Assessment:

N/A

Conclusion: N/A**OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT****Reviewer's Assessment and Signature:**

Rolapitant tablets, 90 mg are immediate release, blue capsule shaped tablets debossed on one side with (b) (4) and 100 on the other side. Each tablet contains 100 mg rolapitant hydrochloride equivalent to 90 mg rolapitant free base.

Rolapitant tablets are indicated for the prevention of (b) (4) delayed nausea and vomiting associated with initial repeat courses of emetogenic cancer chemotherapy. The recommended dose of rolapitant tablets in adults is 180 mg taken orally approximately 1 to 2 hours prior to each chemotherapy cycle on Day 1 in combination with dexamethasone and 1 5-HT3 receptor antagonist.

The inactive ingredients in the tablets are lactose monohydrate, pregelatinized starch, microcrystalline cellulose, povidone (b) (4), croscarmellose sodium, colloidal silicone dioxide and magnesium stearate. The core tablets are (b) (4) with (b) (4) Blue and (b) (4) Clear. All of the excipients in the drug product are compendial and the active drug substance is controlled by internal specification (Sec. 3.2.S.4.1).

The dosage form, selection and amounts of excipients, drug product strength and dosage were based on the results of BA and BE studies, clinical trials and dissolution experiments performed during pharmaceutical development.

The Rolapitant tablets are supplied in ACLAR®/foil blister strips. Each blister contains two 90 mg rolapitant tablets. The to-be marketed product will be supplied in (b) (4)

single dose (b) (4) containing two tablets in a single blister. (b) (4)

The blister is composed of (b) (4) (b) (4) polychlorotrifluoroethylene (ACLAR®). The aluminum foil (b) (4)

The container closure system is adequate (b) (4) during the storage as demonstrated by the stability studies.

The applicant has performed long-term stability up to 12 months and accelerated stability up to 6 months on three registration batches (batch size (b) (4) tablets) to demonstrate that there is no degradation in the product quality during the time tested. Based on satisfactory stability studies results, the 24-month expiration dating period was granted when stored at room temperature.

The specification of rolapitant tablets include tests for description, identification, assay, impurities, dosage uniformity, dissolution, (b) (4) and microbial enumeration. The specification is adequate to assure the identity, strength, purity and quality.

Risk Assessment:

From Initial Quality			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Consideration/ Comments
Assay, stability	• raw materials • process parameters	L	Assay method is satisfactorily validated and it is stability indicating. The long-term and accelerated stability studies of the registration batches confirmed that there is no significant change in the product quality during the time tested.	The drug product is expected to be safe for administration during the entire shelf time from product quality perspective Low to None	None
impurities	• raw materials • process parameters	L	The impurities in the drug product are from the drug substance. All of the impurities are qualified and controlled in the drug product specification. No new drug product process related impurities were observed. The validated HPLC method to determine impurities levels is satisfactory and also stability indicating. In addition, during the stability studies of the registration batches the impurities were within the acceptance limits.	The impurities in the drug product are qualified, well controlled and are within the acceptance limits at release and storage. Thus, the drug product is safe for administration up to 24 months at room temperature. Low to None	

Hitesh Shroff, Ph.D.
Reviewer, Branch V/DNDP II/ONDP

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Supervisor Comments and Concurrence:

I concur with Dr. Hitesh Shroff's assessment on the pharmaceutical quality of 90mg rolapitant tablets packaged in a blister pack (two tablets per pack) that the overall quality control strategy proposed by the applicant, including the specification and stability program, is adequate to assure the identity, strength, purity and quality of the product, thereby assuring the product to provide the same safety and efficacy profile for the patients in managing nausea and vomiting symptom during high or medium emetogenic cancer chemotherapy.

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

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ASSESSMENT OF THE PROCESS**2.3.P DRUG PRODUCT****2.3.P.3 Manufacture**
Batch Formula

21. Does the provided batch formula reflect the proposed composition and that of the registration batches?

Applicant's Response:

The proposed formulation composition under the 3.2.P.1 section is as follows:

Tab. 1. Proposed formulation composition

Component	Quality Grade	Function	Unit Formula (mg/unit)
(b) (4)			
Drug Substance (b) (4)	Internal specifications	(b) (4)	
Lactose Monohydrate	USP/NF, Ph Eur		
Pregelatinized Starch	USP/NF, Ph Eur		
Microcrystalline Cellulose (b) (4)	USP/NF, Ph Eur		
Povidone (b) (4)	USP, Ph Eur		
Croscarmellose Sodium	USP/NF, Ph Eur		
(b) (4)	USP, Ph Eur		
(b) (4)			
Microcrystalline Cellulose (b) (4)	USP/NF, Ph Eur		
Croscarmellose Sodium	USP/NF, Ph Eur		
Colloidal silicon dioxide	USP/NF, Ph Eur		
Magnesium Stearate	USP/NF, Ph Eur		
Film Coating			
(b) (4) Blue	USP/NF, Ph Eur		
Clear	USP/NF, Ph Eur		
Total Tablet Weight		520.0 mg	(b) (4)

The commercial batch formula for a theoretical batch size of (b) (4) is as follows:

Tab. 2. Batch formula

Component	Quality Standard	Purpose	Amount [kg] per Batch
(b) (4)			(b) (4)
Drug Substance	In-House Standard		(b) (4)
Lactose Monohydrate	USP/NF, Ph Eur		(b) (4)
Pregelatinized Starch (b) (4)	USP/NF, Ph Eur		(b) (4)
Microcrystalline Cellulose (b) (4)	USP/NF, Ph Eur		(b) (4)
Povidone (b) (4)	USP/NF, Ph Eur		(b) (4)
Croscarmellose Sodium	USP/NF, Ph Eur		(b) (4)
(b) (4)	USP, Ph Eur		(b) (4)
(b) (4)			(b) (4)
Microcrystalline Cellulose (b) (4)	USP/NF, Ph Eur		(b) (4)
Croscarmellose Sodium	USP/NF, Ph Eur		(b) (4)
Colloidal silicon dioxide	USP/NF, Ph Eur		(b) (4)
Magnesium Stearate	USP/NF, Ph Eur		(b) (4)
(b) (4)			(b) (4)
Tablet Coating			
(b) (4) Blue	Supplier standard		(b) (4)
(b) (4)	USP, Ph Eur		(b) (4)
(b) (4) Clear	Supplier standard		(b) (4)
(b) (4)	USP, Ph Eur		(b) (4)
Total Batch Size			

The registration batch formula extracted by this reviewer from the given executed batch record (Product # 38000004803) is as follows:

Tab. 3. Registration batch formulation composition

Mg/tab	Component	Amount per Batch
		(b) (4)
100.0	Drug Substance (rolapitant API)	(b) (4)
(b) (4)	Lactose Monohydrate	(b) (4)
	Pregelatinized Starch (b) (4)	(b) (4)
	Microcrystalline Cellulose (b) (4)	(b) (4)
	Croscarmellose Sodium	(b) (4)
	Povidone (b) (4)	(b) (4)
	Microcrystalline Cellulose (b) (4)	(b) (4)
	Croscarmellose Sodium	(b) (4)
	Colloidal silicon dioxide	(b) (4)
	Magnesium Stearate	(b) (4)
	(b) (4) Blue	(b) (4)
	(b) (4)	(b) (4)
	(b) (4) Clear	(b) (4)
	(b) (4)	(b) (4)

Reviewer's Assessment: Acceptable.

There is no difference in formulation composition of each ingredient between the proposed formulation composition, commercial batch formula and registration batches. However, the batch size of the registration batch (product # 38000004803) is (b) (4) of the commercial scale. From a regulatory standpoint such (b) (4) from registration to commercial scale is acceptable. Additionally, it is to be noted that for commercial manufacturing, the

(b) (4)

Description of the Manufacturing Process and Process Controls

22. *Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug product batches? (Note: add applicant's response and reviewers assessment box after this question)*

Applicant's response (Includes summary tables and schematics by reviewer)

(b) (4)

specified? What is the method of evaluation of the changes and the acceptance criteria for the change?? How will the changes be reported?

Reviewer's Assessment:

None

OVERALL ASSESSMENT AND SIGNATURES: PROCESS**Reviewer's Assessment and Signature:**

This NDA is recommended for approval from manufacturing process perspective.

Akm Khairuzzaman, Ph.D.

Akm

Khairuzzaman -S

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cn=Akm Khairuzzaman -S
Date: 2015.05.04 09:00:44 -04'00'

Supervisor Comments and Concurrence:

I concur with the recommendation of the process reviewer Dr. Akm Khairuzzaman that the information provided in the application demonstrates that the manufacturing process (b) (4) are adequate to consistently manufacture desired quality product at commercial scale. Additionally, (b) (4)

(b) (4) I am in concurrence with Dr. Khairuzzaman's conclusion

(b) (4)

Sharmista Chatterjee, Ph.D.

Acting Branch Chief, Branch I/DPA I/OPF

Sharmista

Chatterjee -S

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ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

25. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Current status	Final Recommendation
(b) (4)					

Reviewer's Assessment:

Initial Facility Risk Assessment for the sites involved in drug substance manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk
(b) (4)							

The drug substance manufacturing facility (b) (4) was last inspected in 4/2013 and has a history of NAI inspections covering the CSN profile (i.e. (b) (4)).

While this drug substance is a New Molecular Entity, (b) (4)
(b) (4)

are defined. The overall control strategy appears appropriate and the manufacturing operations are supported by development studies.

(b) (4)

(b) (4) is acceptable based its inspection history. Post-approval inspectional coverage of rolapitant is recommended for (b) (4) so that in process testing results can be assessed, operation within the (b) (4) can be confirmed, (b) (4)

(b) (4)
and release and stability testing of the drug substance. This facility was last inspected 9/2013 and has a history of NAI & VAI inspections covering (b) (4)

(b) (4)
Since a surveillance inspection was already planned for this facility at the time NDA 206500 was received, focused pre-approval inspectional coverage was provided on-site for the physical characterization and analytical evaluation of rolapitant (b) (4)

(b) (4)
During inspectional review of the rolapitant API assay and related substances HPLC method, it was determined that an unknown impurity (b) (4)

(b) (4). This method had been approved (b) (4). In their response, (b) (4)

(b) (4)
not a specified impurity, it was not required to be evaluated as part of the validation selectivity criteria. The firm committed to redoing the method validation and is taking this opportunity to include some additional elements to enhance the quality of the method (b) (4)

(b) (4)
validation protocol was provided and is acceptable.

While a CAPA was issued a year later following deviation #26014, it was determined that the investigation failed to establish a root cause for an assay OOS and therefore the corrective or preventive action was inadequate. The firm response stated that a full investigation determined that an "unclear procedure" for sample preparation resulted in a dissolution problem leading to the OOS result. An optimization study for improved sample preparation was created and the best method as determined by this study will be included as part of the analytical method validation proposed to address Observation 2 above. This sample preparation study protocol was provided and is acceptable.

The firm's response to the December 1-5, 2014 pre-approval and cGMP inspection appears adequate. This facility inspection received an initial VAI cGMP classification. Therefore, **this facility is acceptable based on the inspectional outcome** for NDA

206500.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Manufacturer(s)

26. *Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?*

Establishment name	FEI Number	Responsibilities and profile code	Initial Risks Identified	Current status	Final Recommendation (b) (4)

Reviewer's Assessment:

Initial Facility Risk Assessment for the site involved in drug product manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment (b) (4)

medium facility risks were identified for the New Molecular Entity drug product manufacturer and so a pre-approval inspection was conducted.

Compression Operational Parameters

rolapitant specific Form 483 observations and received a VAI cGMP classification. A review of the Jan 26-30, 2015 pre-approval and cGMP inspection determined that **this facility is acceptable** for NDA 206500.

(b) (4) will be completing drug product microbiological testing for release and stability material. This facility was last inspected 9/2013 and was found to be acceptable for these testing operations. Rolapitant pre-approval coverage is not required. **This facility is acceptable based on inspectional history.**

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application. Based on firm inspectional history and data reviewed during the pre-approval inspections, the manufacturing facilities as listed above for NDA 206500 are found to be acceptable.

Post-approval inspectional coverage is recommended for drug substance manufacturer:

(b) (4)
Christina Capacci-Daniel, Ph.D.
Consumer Safety Officer, OPQ/OPF/DIA/IABII

**Christina
A. Capacci-
daniel -S**
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Date: 2015.05.01 12:56:09 -04'00'

Supervisor Comments and Concurrence:

I concur with this Facility Assessment.

Mahesh Ramanadham, PharmD, M.B.A., RPh.
Acting Branch Chief, OPQ/OPF/DIA/IABII

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ASSESSMENT OF THE BIOPHARMACUETICS

27. *Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?*

28. *Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?*

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Dissolution method and proposed dissolution acceptance criteria

The sponsor claims that Rolapitant can be classified as a BCS II compound.

(b) (4)

(b) (4)

During the drug development, a series of formulations were developed including 50 mg capsule, 100 mg tablet formulation by Schering-Plough, (b) (4) and the 100 mg tablet to be market formulations. A design of experiments (DoE) approach was applied with dissolution as the end point to help the formulation development. Since in the three Phase 3 chemotherapy-induced nausea and vomiting (CINV) clinical studies, a formulation of 50 mg capsule was applied, bioequivalence studies PR-10-5013-C and PR-10-5014-C were conducted to bridge the tablet and capsule formulations.

The final composition for the formulation in the early drug development and the final commercial formulation are shown in Table 1.

Table 1: Composition of Formulations for Clinical BA and BE Studies

Formulation		50 mg capsule	100 mg tablet (Schering)	(b) (4)		100 mg tablet	100 mg tablet (b) (4)	100 mg tablet (commercial)							
Clinical study ^a	Study number	Phase I/II/III	P05325	PR-10-5000-C		PR-10-5007-C		PR-10-5013-C PR-10-5014-C							
	Results/comments (BE reference is 50 mg capsule)	N/A	Low BA ^b	Low BA ^b	Low BA ^b	BE	BE	BE							
(b) (4)															
Composition (b) (4)		[mg]	[wt%]	[mg]	[wt%]	[mg]	[wt%]	[mg]	[wt%]	[mg]	[wt%]	[mg]	[wt%]	[mg]	[wt%]
Drug Substance		(b) (4)													
Lactose Monohydrate		(b) (4)													
Pregelatinized Starch		(b) (4)													
Microcrystalline Cellulose (b) (4)		(b) (4)													
Povidone (b) (4)		(b) (4)													
Croscarmellose Sodium (b) (4)		(b) (4)													
Microcrystalline Cellulose (b) (4)		(b) (4)													
Croscarmellose Sodium		(b) (4)													
Colloidal silicon dioxide		(b) (4)													
Magnesium Stearate (b) (4)		(b) (4)													
Blue (b) (4)		(b) (4)													
Clear (b) (4)		(b) (4)													
Total core/fill		(b) (4)													

The specification and dissolution acceptance criterion are shown in Table 2.

Test	Method		Acceptance Criteria
	Type	Code	
Description	Visual	CTMLP-3149	Blue modified capsule shaped tablet debossed on one side with T0101 and 100 on the other. Color conforms to standard.
Identification	UV	CTMLP-3019	The UV spectrum conforms to that of the reference standard
Identification	HPLC	CTMLP-3019	The retention time of the rolapitant peak in the sample preparation corresponds to that of the standard preparation
Assay	HPLC	CTMLP-3019	(b) (4) % of the label claim
Impurities/Degradation Products	HPLC	CTMLP-3019	Individual: NMT (b) (4) % Total: NMT (b) (4) %
Uniformity of Dosage Units	USP<905> and HPLC	CTMLP-3019	Meets USP requirements
Dissolution	USP<711> Apparatus 2 with HPLC determination	CTMLP-3185	$Q = \frac{(b) (4)}{(4)}$ % of label claim at 30 minutes
(b) (4)			
Microbial Enumeration ^a	Compendial	USP <61> and <62>	Total Aerobic Microbial Count: NMT (b) (4) cfu/g Total Combined Molds and Yeast Count: NMT (b) (4) cfu/g <i>Escherichia coli</i> : Absent in (b) (4)

^a Microbial testing per USP<61>/<62> is proposed for validation and stability batches only

(b) (4)

and the Applicant would use dissolution method-3 as the final QC dissolution method. The difference and comparison of three different dissolution methods are shown in Table 3.

Table 3: Different dissolution methods developed by the Applicant during the pharmaceutical development

	(b) (4)	Dissolution Method-3 (QC method)
Parameter		Setting
Apparatus		USP Apparatus 2 (paddles)
Speed		50 rpm and raised to 250 rpm at 60 min
Temperature		37°C ± 0.5°C
Dissolution Medium		0.05M sodium acetate buffer, pH 4.0
Dissolution Volume		900 mL
Dose per vessel		100 mg (1x 100 mg Tablet)
Filters		(b) (4)
Sampling times		5, 10, 15, 30, 45, and 60 min and retaken at 75 min after the raise of paddle speed to 250 rpm at 60 min

Data to support the bridging across phases

The formulations used in the three Phase-3 clinical trials are 50 mg capsule. A 100 mg (b) (4) tablet was developed by Schering-Plough and evaluated in bioavailability study (P0484) to compare to the 50 mg capsule. Although the two formulations showed

(b) (4)

Then, the Applicant followed a DoE approach by using the dissolution as the end-point to examine various aspects including excipient selection and levels, manufacturing process options, and the dosage forms of tablets and capsules. Follow this approach, two prototypes of (b) (4) IR 100 mg (b) (4) tablets and 100 mg (b) (4) tablets were developed, and they were shown to be comparable to the 50 mg capsule formulation by the bioavailability study PR-10-5007-C. Based on the manufacturing considerations, the (b) (4) (b) (4) tablet was finally selected as the final commercial drug product.

The final commercial formulation was determined to be blue film coated, which was identical to the 100 mg (b) (4) tablet (b) (4). To bridge this commercial formulation to the reference formulation 50 mg capsules used in the clinical trials, bioequivalence studies (b) (4) and PR-10-5014-C were conducted by the Applicant to evaluate the bioequivalence of this 100 mg (b) (4) blue film coated tablets and the 50 mg capsules. The PR-10-5013-C failed to meet the bioequivalence to the 50 mg capsules. The Applicant concluded the failure to clinical trial design, and in the following PR-10-5014-C study, the Applicant designed the study to be more stringent and better controlled with the in-house stay (b) (4) 38 days following the oral administration of the dose regimens, (b) (4) (b) (4). The PR-10-5014-C proved the bioequivalence between final commercial formulation and the reference 50 mg capsule formulation.

As a summary, the submission provided the data supporting the bridging of formulations across the different phases, and the final commercial formulation is bioequivalent to the 50 mg capsules used in the Phase 3 clinical trials.

Reviewer's Assessment:

1. Dissolution methods

Dissolution testing as a function of pH over the entire physiologically relevant range has not been performed on the rolapitant hydrochloride 100 mg tablet. The solubility of Rolapitant

(b) (4)

Figure 1. Development of Final QC Dissolution Method (Method 3) Using the Intended Commercial Drug Product Formulation (Batch # KKXB) – Effect of Dissolution Method Variables

(b) (4)

Table 4: Dissolution Variables Tested During Development of Final QC Dissolution Method (Method-3)

(b) (4)

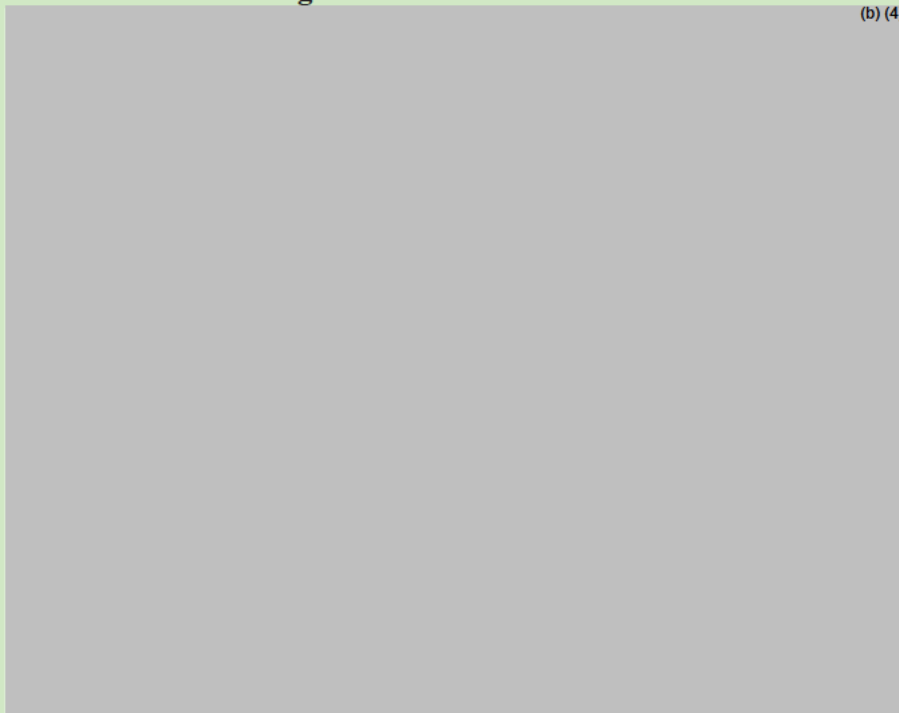
Method-3 was not tested in the whole range of pH, the solubility of Rolapitant hydrochloride monohydrate is the highest at (b) (4) and decreased exponentially with (b) (4) was tested and compared. Dissolution media in the final QC dissolution method-3 is at pH 4, (b) (4)

(b) (4) the dissolution in USP 2 for all conditions evaluated is almost complete in the period tested (Fig 1). (b) (4) USP 2 is selected

as the apparatus. Release at pH 4.0, (b) (4) thus this condition was selected for the discriminability.

Method-3 was tested for robustness with tablets manufactured using a range of process conditions (Fig 2).

Figure 2 Development of Final QC Dissolution Method (Method 3) – Robustness to Tablet Manufacturing Process



Results (Fig 2) showed similar dissolution profiles for (b) (4) tablets, which was consistent with their in vivo exposure as BA results (Study PR-10-5007- (b) (4)

The dissolution of rolapitant is measured by HPLC. The Applicant provided the method validation report for the determination of dissolution release of 50 mg capsule and 100 mg tablets by HPLC (report# TES-AR-018-0613-R0 (PART A)). Overall, the validation is acceptable. Due to the (b) (4) of 50 mg capsules, the Applicant only evaluated (b) (4) the 50 mg capsules. The Applicant indicated (b) (4)

The Applicant should submit (b) (4) which is not found in the NDA submission. to us for review once it is ready.

Overall, the proposed dissolution method-3 as QC dissolution method is acceptable, and it shows some discriminability over some key manufacturing parameters.

2. Dissolution acceptance criterion

The proposed acceptance criterion is $Q = \frac{(b)}{(4)}\%$ of label claim at 30 minutes. Dissolution testing is performed as both a release and stability requirement using a discriminating final QC dissolution method-3 specifically developed for this product. Dissolution method-3 was also used in three registration lots (KXWB, KXVY, and KXVZ) to generate the dissolution profiles data (Applicant's tables 1-3). Fig 3 showed the dissolution profiles of three registration batches with dissolution method 3.

Table 1: Dissolution Profile Data for Printed Rolapitant Hydrochloride Monohydrate 100 mg Tablets Packaged Batch MPVW (Bulk KXVY) (Method-3)

(b) (4)



Table 2: Dissolution Profile Data for Printed Rolapitant Hydrochloride Monohydrate 100 mg Tablets Packaged Batch MPVX (Bulk KXVZ) (Method-3)

(b) (4)



Table 3: Dissolution Profile Data for Printed Rolapitant Hydrochloride Monohydrate 100 mg Tablets Packaged Batch MPVY (Bulk KXWB) (Method-3)

(b) (4)



Figure 3 Dissolution profiles data of three registration batches KXVY, KXVZ, and KXWB by using dissolution method 3 (reviewer's own plot, error bar represents min and max of drug release at each time point indicated)

(b) (4)

The dissolution profiles reveal that the drug release (b) (4) the drug release in most batches (KXVY and KXWB) (b) (4). Therefore, there is a possibility that $Q = \frac{(b)(4)}{(4)}\%$ could be set at 20 min. On 02/05/2015, an IR was sent to the Applicant asking them to include 20 min in the dissolution time profiles:

To obtain the complete dissolution profile data, an additional sampling time point at 20 minutes (i.e., at 15, 20, 30, 45, and 60 minutes) should be collected in order to set the final dissolution acceptance criterion. Provide the complete dissolution data (including individual; n=12, mean, and standard deviation) and mean dissolution profiles for the above three lots for review.

In response, the Applicant provided following justifications:

The timepoints selected adequately characterize the dissolution curve of this formulation. The timepoints of 5, 10, 15, 30, 45, and 60 minutes are consistent with the suggested sampling time intervals (i.e. 15 minute intervals) cited as examples in "Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms" for a BCS class II compound. TESARO validated the described Method-3 as submitted to the NDA (please see sections 3.2.P.2.2.1.4, 3.2.P.5.2.2.5 and 3.2.P.5.3.2.5), and has applied this method without a 20-minute collection point for our registration stability batches. Furthermore, the proposed QC method (Method-3), with the time-points defined above, is believed to be an appropriately discriminating method for release of the product.

The release of rolapitant 100 mg tablets at 30 min was also tested during the stability test in three-registration batches #MPVW, #MPVX, and #MPVY. Figure 4 showed the release of rolapitant at 30 min for each batch at different time period tested.

Figure 4 Release of rolapitant tablets at 30 min for stability test with batch MPVW, MPVX, and MPVY stored at 25°C/60% RH (Dissolution method-3) (reviewer's own plot, error bar represents min and max of drug release at each time point indicated)

(b) (4)

Registration stability batches met the acceptance criteria with dissolution at 30 minutes as Figure 4 showed up to 12 month of storage at 25°C/60% RH. The fluctuation of drug release during the completely tested stability period is small, and keeps at the range between (b) (4) up to 12-month stability test at 25°C/60% RH. The release during the stability test met

(b) (4)

Based on the totality of drug dissolution profile data (Fig 3) and drug release data during stability test (Fig 4), the specification of $Q = \frac{(b)}{(4)}\%$ of label claim at 30 minutes is considered appropriate.

In the dissolution method-3, the Applicant raises the rotation speed to 250 rpm at 60 min and takes samples at 75 min. (b) (4) min. Therefore, an IR was sent on 4/21/2015 to the Applicant as follows for the clarification.

FDA Request:

Your submission states that QC dissolution method is as follows:

The method employs Apparatus 2 (paddles), a dissolution medium of 50 mM sodium acetate buffer, pH 4.0 thermostatted at 37°C with a paddle rotation speed of 50 rpm. After inserting a tablet in each of six vessels, samples of the dissolution medium are withdrawn from each vessel at intervals of 5, 10, 15, 30, 45, and 60 minutes. At 60 minutes the paddle speed is raised to 250 rpm and a sample is taken at 75 minutes.

Clarify:

1. The volume of the dissolution medium.
2. Purpose of "At 60 minutes the paddle speed is raised to 250 rpm and a sample is taken at 75 minutes."

Applicant Response:

The volume of the dissolution medium is 900 mL.

The purpose of the 75 minute sampling point (where the paddle speed is raised to 250 rpm at 60 minutes) is to ensure that the entire contents of the tablet are dissolved.

Thus, the 75 minute time point represents dissolution at time infinity (t_{∞}).

The dissolution specification is (b) (4)% at 30 min and is acceptable based on the data above. Therefore, raising speed to 250 rpm after 60 min will not affect the acceptance of dissolution method and specification.

3. Data to support the bridging the formulations across phases

The formulations used in the three Phase-3 clinical trials are 50 mg capsule. The final commercial formulation was determined to be blue film coated, which was identical to the 100 mg (b) (4) tablet (b) (4). Table 5 shows the lots representative of the commercial 100 mg tablet formulation.

Table 5. Lots representative of the Commercial 100 mg Core Tablet Formulation Composition

Manufacturer	Lot	Description
(b) (4)	FT12069	(b) (4)
	FT12113	
	FT12103	
	PD12180	
	KKXB	
	KXWB	
	KXVY	
	KXVZ	

To bridge this commercial formulation to the reference formulation 50 mg capsules used in the clinical trials, bioequivalence studies PR-10-5013-C and PR-10-5014-C were conducted by the Applicant to evaluate the bioequivalence of this 100 mg (b) (4) blue film coated tablets and the 50 mg capsules.

3.1 Review of Bioequivalence study PR-10-5013-C

The primary objective of this study was to assess the bioequivalence of a (b) (4)

(b) (4)

(b) (4)

Group		Safety (n/N)	Pharmacokinetics (n/N)
(b) (4)			

The batch information for administrated drugs are shown as following table:

Treatment	Drug Name	Formulation	Dose and Strength	Dosing Conditions	Route	Lot No.
(b) (4)						

(b) (4)

Besides study 10-5013C, the Applicant conducted other two separate clinical studies to study the food effect on Rolapitant. Study P03670 studied the food effect on clinical trial formulation 50 mg capsules. The consumption of high fat meal weekly reduce the rate of absorption by delaying the T_{max} of rolapitant from 3 hrs in the fast condition to 5 hr in the fed condition. However, the overall exposure was not affected by food (Table 14 from the Applicant).

Table 14: Rolapitant Pharmacokinetics Parameters Following Single-Dose Oral Administration of 50 mg Rolapitant in the Fed and Fasted Condition to Healthy Volunteers (P03670)

Dose (mg)	N	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Fasted	8	276 (24)	3 (1.5-4)	33600 (42)	171 (28)
Fed	6	276 (18)	5 (3-12)	35300 (29) ^a	167 (23) ^a

Source: CSR P03670, Table 22.

Presented as Mean (% CV) with T_{max} as Median (Range)

AUC = area under the plasma concentration-time curve; C_{max} = maximum concentration; CV = coefficient of variation; N = number; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum concentration.

^a N = 5

Study P04854 studied the food effect on 100 mg rolapitant IR (b) (4) tablet developed by the Schering-Plough (b) (4). There was a slight increase of ~24% in C_{max} in the fed state compared to that in the fast state, while the AUC inf was not significantly changed as shown by the Applicant in Table 15.

Table 15: Rolapitant Pharmacokinetics Parameters Following Single-Dose Oral Administration of 100 mg Rolapitant in the Fed and Fasted Condition to Healthy Volunteers (P04854)

Dose (mg)	N	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-120} (ng·hr/mL)	AUC_{0-t} (ng·hr/mL)	$t_{1/2}$ (hr)
Fasted	12	537 (14)	3.5 (3-6)	28600 (16)	73000 (29)	170 (26) ^a
Fed	11	667 (17)	4 (3-6)	31000 (15)	74100 (20)	163 (20) ^a

Source: CSR P04854, Table 21.

Presented as Mean (% CV) with T_{max} as Median (Range)

AUC = area under the plasma concentration-time curve; CI = confidence interval; C_{max} = maximum concentration; CV = coefficient of variation; N = number; NC = not calculated; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum concentration.

^a N = 6

Furthermore, based on dose-response study in P04351, rolapitant at the dose of 200 mg was expected to occupy ~90% of NK1 receptor, and rolapitant was safe and well tolerated at 10, 25, 100, and 200 mg while administrated as a single dose 2hr prior to chemotherapy in subjects receiving HEC for up to six cycles. A dose-dependent relationship among treatment groups in the overall incidence of these adverse events or of serious adverse events was not observed.

Although in study 10-5013C, (b) (4)

Because of the failure of PR-10-5013-C in the establishment of bioequivalence between the tablet and capsule formulations, the Applicant conducted another bioequivalence trial PR-10-5014-C.

3.2 Review of Bioequivalence study PR-10-5014-C

The primary objective of this study was to assess the bioequivalence of a single oral dose of 200 mg Rolapitant administrated in a commercial formulation 2x 100 mg tablets versus clinical trial formulation 4x 50 mg capsule.

This is an open-label randomized parallel design bioequivalence study. The treatment and the drug administrated are shown in following tables.

Group		Safety	Pharmacokinetics
Treatment A (4 x 50 mg rolapitant capsules)	Enrolled	43	43
	Evaluable	43	42
Treatment B (2 x 100 mg rolapitant tablets)	Enrolled	44	44
	Evaluable	44	42

(b) (4)

The batch information for administrated drugs are shown as following table:

Test Product and Dose:

Study Drug Name	Formulation	Strength	Dose	Lot No.
Treatment A	Capsule	50 mg	200 mg	PD12053
Treatment B	Tablet	100 mg	200 mg	4800004710-NZDF

(b) (4)

The lot no. for the test tablet formulation is different as that in the study 1053C.

The Applicant claimed that they were all from one of the registration stability batch KXVY.

In study Day 1, subjects in treatment A and B were required to fast overnight and for an additional 4 hours postdose. Blood samples for PK analysis were collected on Day 1 predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 120, 168, 240, 312, 384, 456, 504, 576, 672, 792, 912 hrs postdose.

Study PR-10-5014-C applied the (b) (4) analytical validation reports and the bioanalytical reports are acceptable.

(b) (4)

Analysis of bioequivalence for rolapitant plasma PK parameters was shown in following table:

TESARO, Inc.
PR-10-5014-C

Page 1 of 1

Table 14.2.3.1
Parametric Analysis of Relative Bioequivalence for Rolapitant Plasma Pharmacokinetic Parameters in Fasted State Pharmacokinetic Population

Parameter	Treatment	N [1]	n [2]	Geometric LS Mean	Geometric LS Means 95% CI	Ratio (B/A)	90% CI for Ratio of Geometric LS Means
C _{max} (ng/mL)	A (reference)	84	42	936.12	(853.33, 1026.95)	0.99	(0.89, 1.11)
	B		42	930.05	(847.79, 1020.28)		
AUC _{0-t} (ng.h/mL)	A (reference)	84	42	112836.54	(102156.57, 124633.05)	1.06	(0.94, 1.19)
	B		42	119123.61	(107848.57, 131577.41)		
AUC _{0-inf} (ng.h/mL)	A (reference)	84	42	117397.45	(105439.90, 130711.06)	1.05	(0.92, 1.19)
	B		42	122998.46	(110470.42, 136947.26)		
AUC ₀₋₁₂₀ (ng.h/mL)	A (reference)	84	42	46409.73	(42939.41, 50160.52)	1.06	(0.97, 1.17)
	B		42	49338.31	(45649.00, 53325.79)		

Reviewer conducted his own BE analysis and results were shown as below, despite slight difference in the estimation of the geometric LS means of each PK parameter, the ratio and 90% CI were generally consistent with the Applicant's analysis. Bioequivalence was established for the test commercial 1x100 mg tablet formulation with the clinical trial 50 mg capsule formulation.

For m Ref	Dependent	Test				
		B				
		Ratio_ %	CI_90_Low er	CI_90_Upp er	Test GeoLSM	RefGeoLSM
A	Ln(AUC ₀₋₁₂₀)	106.31	96.97	116.54	49306.53	46380.31
A	Ln(AUCINF_pre d)	104.82	92.37	118.96	122663.6 1	117022.46
A	Ln(AUClast)	105.54	93.85	118.69	118912.0 3	112669.26
A	Ln(C _{max})	99.35	89.04	110.85	930.05	936.12

Overall Reviewer's Assessment:

The BE study 10-5013C failed to meet the BE criteria, and the reason the Applicant concluded was (b) (4) in study 10-5014C, after administration of drugs, subjects stayed in house for 38 days; (b) (4)

The sponsor's justification for the failure of BE criteria in Study 10-5013C is acceptable by the reviewer. The results from 10-5014C is acceptable, and thus, the commercial formulation 100 mg tablet is considered bioequivalent to clinical trial formulation 50 mg capsule.

3.3 Data bridging the printed and debossed rolapitant tablets

The three registration batches (KXVY, KXVZ, and KXWB) are (b) (4) while in the final commercial batches, the tablets will be debossed for identification without any ink. In response to the IR question 2 sent to the Applicant on Feb 6, 2015, the Applicant provided the data support the dissolution similarity between (b) (4) tablets either based on dissolution profile shown in Fig 5 and based on the f2 values shown in Table below.

Fig 5 Comparative Dissolution Profiles for (b) (4) Rolapitant Tablets (Method-3)

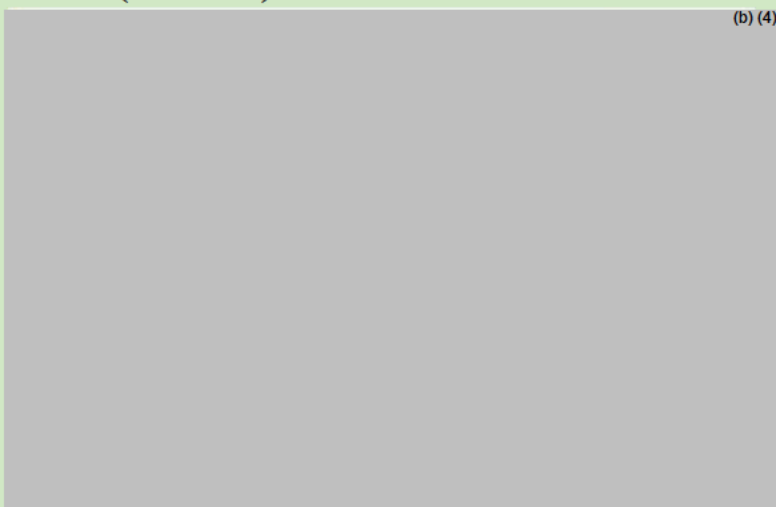


Table: f2 calculations for dissolution profile comparison between (b) (4) batch PXMS Vs (b) (4) batches MPVW, MPVX, and MPVY (Reviewer's own calculation)

Dissolution comparison	f2 values
(b) (4)	

Based on the dissolution profiles comparison and f2 calculations, the (b) (4) tablets showed similar dissolution profiles.

Overall, the data submitted by the Applicant support the bridging of the formulations to final commercial formulations.

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS****Reviewer's Assessment and Signature:**

The dissolution method as described below and proposed acceptance criterion ($Q = \frac{(b)}{(4)}\%$ at 30 min) are acceptable for both release and stability.

Parameters	Setting
Apparatus	USP Apparatus 2(paddles)
Speed	50 rpm and raised to 250 rpm at 60 min
Temperature	37°C ± 0.5°C
Dissolution Medium	0.05M sodium acetate buffer, pH 4.0; 900 mL
Sampling Time points	5, 10, 15, 30, 45, and 60 min and retaken at 75 min after the raise of paddle speed to 250 rpm at 60 min

The bioequivalence study PR-1054-C is acceptable and supported the bridging of clinical formulation 50 mg capsules to the final commercial formulation 100 mg tablet. From the Biopharmaceutics perspective, NDA 206500 is recommended for approval.

Peng (Vincent) Duan, Ph.D.
OPQ/ONDP/DB/Branch II

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Duan -S

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ou=HHS, ou=FDA, ou=People,
cn=Peng Duan -S
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Supervisor Comments and Concurrence:

The Dissolution method and proposed acceptance criterion ($Q = \frac{(b)}{(4)}\%$ at 30 min) are acceptable. The bridging of clinical formulation 50 mg capsules to the final commercial formulation is adequate. The supervisor concurs with the reviewers comments.

Tapash Ghosh, Ph.D.
Branch Chief, OPQ/ONDP/DB/Branch II

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Ghosh -S

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ASSESSMENT OF MICROBIOLOGY

29. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Reviewer's Assessment:

Not Applicable as this product is not a sterile product.

30. *Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?*

Reviewer's Assessment:

N/A

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

31. *Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?*

Reviewer's Assessment:

The tablets contain bovine derived lactose monohydrate as one of the excipients, and the applicant states that it complies with all Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE) applicable US and EU regulations. A certificate of analysis to that effect was submitted.

32. *If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?*

Reviewer's Assessment:

See the above statement.

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

33. Is the applicant's claim for categorical exclusion acceptable?

In accordance with 21 CFR 25.31(b), the applicant submitted a claim for a categorical exclusion since the estimated concentration of rolapitant hydrochloride monohydrate at the point of entry into the aquatic environment will be below a concentration of 1 part per billion (ppb), as calculated in the application (b) (4)

Reviewer's Assessment: Acceptable.

The categorical exclusion claim is appropriate for this application. The anticipated amount of drug to be used, and the calculation is accurate. The expected introduction concentration (EIC) is almost (b) (4) orders of magnitude below the 1 ppb categorical exclusion value. In response to new draft guidance, *Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity* (FDA 2015), clinical and nonclinical data and the literature were reviewed for any signals of estrogenic, androgenic, or thyroid activity. No signals were found, and a statement of no extraordinary circumstances is present. The categorical exclusion claim is acceptable.

James P. Laurenson, ONDP/EA Team

James P.

Laurenson -S

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Supervisor Comments and Concurrence:

I concur.

Scott Furness, Deputy Director, ONDP

Michael S.

Furness -S

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I. Review of Common Technical Document-Quality (Ctd-Q) Module 1***A. Labeling & Package Insert*****a) Carton and Container Labels****Immediate container label**

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The established name is not presented correctly. Not Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(b) (4) equivalency statement not present Not Satisfactory
Net contents (21 CFR 201.51(a))	Not displayed Not Satisfactory
“Rx only” displayed prominently on the main panel	The statement is not displayed due to lack of space. However, it is on the carton label. Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is not indicated due to lack of space. However, it is on the carton label as NDC (b) (4) Satisfactory
Lot number and expiration date (21 CFR 201.17)	Displayed Satisfactory

Storage conditions	Storage condition is not displayed due to lack of space on this label. However, it is displayed on the carton label. Satisfactory
Bar code (21CFR 201.25)	Barcode is not displayed due to lack of space on the label. However, it is displayed on the carton label. Satisfactory
Name of manufacturer/distributor	The name of manufacturer is not displayed due to lack of space on this label. However, it is displayed on the carton label. Satisfactory
And others, if space is available	N/A

Evaluation: Not adequate. The drug name on the immediate container label is recommended to be revised as follows:

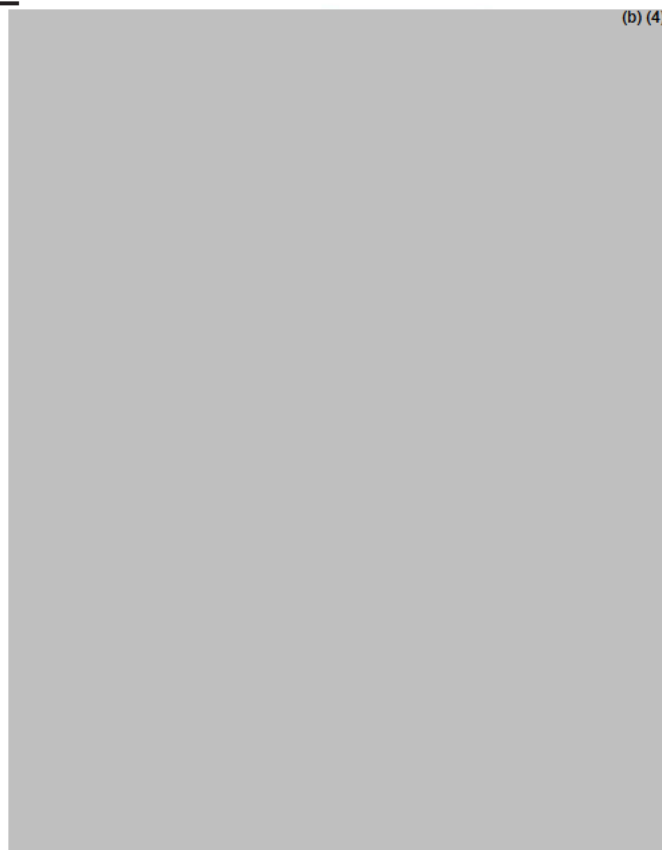
Varubi
(rolapitant) tablets
*90 mg**
**(equivalent to 100 mg rolapitant hydrochloride)*

The applicant provided a (b) (4) [redacted] The information provided on both labels is inadequate. The applicant should submit immediate container and container labels (b) (4) [redacted]

The immediate carton and container labels should be revised as follows:

- The drug product name should be displayed as shown below:
Varubi
(rolapitant) tablets
*90 mg**
**(equivalent to 100 mg rolapitant hydrochloride)*
- Display total number of tablets per carton e.g. “2 tablets”

Carton label



Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size, prominence) (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name and established name are not correctly described. Not Satisfactory
Dosage strength (21CFR 201.10(d)(1), 21CFR 201.100(b)(4))	Not correctly displayed Not Satisfactory
Net quantity of dosage form (21 CFR 201.51(a))	Not correctly displayed Not Satisfactory
“Rx only” displayed prominently on the main panel (21 CFR 201.100 (b)(1))	The statement is prominently displayed. Satisfactory
Expiration date and lot number (21 CFR 201.17 and 21 CFR 201.18)	A space is allocated for this information. Satisfactory
Storage conditions	Storage condition is not correctly described. USP storage statement should be added. Not Satisfactory
Bar code (21CFR 201.25)	Is displayed Satisfactory
NDC number (21 CFR 201.2, 21 CFR 207.35(b)(3)(i))	NDC number is indicated as NDC (b) (4)

	Not Satisfactory
Manufacturer/distributor's name 21CFR201.1(a)	The name of manufacturer is correctly described. Satisfactory
The list of inactive ingredients, 21CFR 201.10(a), if not oral dosage form; and quantitative ingredient information, if parenteral injection. 21CFR 201.100(b)(5)(iii)	The inactive ingredients are not displayed Not Satisfactory
Statement of being sterile (if applicable)	N/A
"See package insert for dosage information" (21 CFR 201.55)	Refer to package insert for dosing information Satisfactory
(b) (4)	Displayed Satisfactory
Route of Administration (21 CFR 201.100(b))	N/A

Evaluation: (b) (4)

- The drug product name should be displayed as shown below:
Varubi
(rolapitant) tablets
*90 mg**
**(equivalent to 100 mg rolapitant hydrochloride)*
- Revise the storage statement as shown below:
Store at 20° to 25°C (68° to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]
- The inactive ingredients should be listed
- Display total number of tablets per carton e.g. "2 tablets"

b. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION
 These highlights do not include all the information needed to use BRAND NAME safely and effectively. See full prescribing information for BRAND NAME.
 BRAND NAME (rolapitant hydrochloride) tablets, for oral use
 Initial U.S. Approval: <<Insert four-digit year>>

DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	BRAND NAME(Rolapitant (b) (4) tablets, for oral use	Proprietary name is not approved yet. The established name is not described correctly. Not Satisfactory
Dosage form, route of administration	Tablets (b) (4)	Satisfactory
Controlled drug substance symbol (if applicable)		Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets (b) (4) mg rolapitant (b) (4)	The dosage form is described as tablets is correct. The strength is not described correctly. The strength should be based on rolapitant free base and an equivalency statement should be added per FDA salt policy. Not Satisfactory
Whether the drug product is scored (If the product is not scored, do not say "not scored.")		The product is not scored.

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3. DOSAGE FORMS AND STRENGTHS

(b) (4)

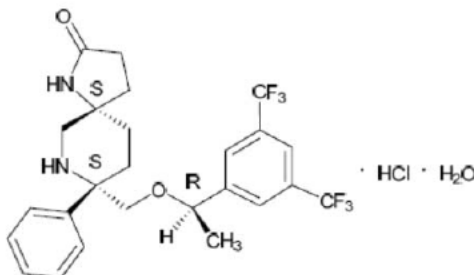
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Dosage form described correctly. Satisfactory

Strengths: in metric system	(b) (4) mg rolapitant (b) (4)	The strength is not described correctly. The strength should be based on rolapitant free base per FDA salt policy. Not Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Film-coated blue tablets, debossed with T0101 on one side and 100 on the other side	The tablets are described correctly. Satisfactory

#11: Description (21CFR 201.57(c)(12))

11. DESCRIPTION

(b) (4)
(b) (4) a substance P/neurokinin 1 (NK1) receptor antagonist, chemically described as (5S,8S)-8-[[[(1R)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-methyl]-8-phenyl-1,7-diazaspiro[4.5]decan-2-one hydrochloride monohydrate. Its empirical formula is (b) (4) and its structural formula is:



Rolapitant hydrochloride is a white to off-white powder, with a molecular weight of 554.95. Solubility of rolapitant hydrochloride in aqueous solution is pH dependent and is more soluble at lower pH. Rolapitant hydrochloride has good solubility in common pharmaceutical solvents such as ethanol, propylene glycol, and 40% hydroxypropyl beta cyclodextrin.

Each tablet for oral administration contains (b) (4) and the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, Povidone, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The tablets are coated in non-functional blue and clear coats. The tablet coating comprises the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue No. 2-Indigo Carmine Lake and polysorbate 80.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	BRAND NAME (Rolapitant) (b) (4) tablets	Proprietary name is not approved yet. The established name is not described correctly. Not Satisfactory
Dosage form and route of administration	Tablets	Satisfactory

If radioactive, statement of important nuclear characteristics.		Not applicable
Active moiety expression of strength with equivalence statement for salt (if applicable)	(b) (4)	Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, povidone, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The tablet coating comprises the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue No. 2-Indigo Carmine Lake and polysorbate 80.	Information for inactive ingredients is provided correctly. Satisfactory
Statement of being sterile (if applicable)		Not applicable
Pharmacological/ therapeutic class	substance P/neurokinin 1 (NK1) receptor antagonist	It will be determined in the labeling meetings.
Chemical name, structural formula, molecular weight	(b) (4)	

Other important chemical or physical properties (such as pKa, solubility, or pH)	Rolapitant hydrochloride is a white to off-white powder, with a molecular weight of 554.95. Solubility of rolapitant hydrochloride in aqueous solution is pH dependent and is more soluble at lower pH. Rolapitant hydrochloride has good solubility in common pharmaceutical solvents such as ethanol, propylene glycol, and 40% hydroxypropyl beta cyclodextrin.	The appearance and the solubility of the drug substance in various solvents is described. Satisfactory
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#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))**16. HOW SUPPLIED/STORAGE AND HANDLING**

BRAND NAME tablets are film-coated blue tablets, debossed with T0101 on one side and 100 on the other side. BRAND NAME tablets are packaged in an Aclar blister shell with aluminum foil backing and supplied as follows:



A single dose package (2 tablets as one set of twinned blisters)

Storage

Store at 20-25°C (68-77°F); excursions are permitted (b) (4) 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Not listed	This information is not provided. Not satisfactory
Available units (e.g., bottles of 100 tablets)	(b) (4)	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	BRAND NAME tablets are film-coated blue tablets, debossed with T0101 on one side and 100 on the other side. BRAND NAME tablets are packaged in an Aclar blister shell with aluminum foil backing and supplied as follows: (b) (4)	The tablets shape and NDC numbers are not provided. Not satisfactory
Special handling (e.g., protect)		Not applicable
Storage conditions	Store at 20-25°C (68-77°F); excursions are permitted (b) (4) 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]	Information provided correctly. Satisfactory

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		Information not provided. Not satisfactory

II. List of Deficiencies To Be Communicated

A. Regarding EA assessment

A final recommendation on the Environmental Assessment from the EA Review Staff has not been made.

B. Regarding immediate container and carton labels

1. The immediate carton (b) (4) should be revised as follows:

- The drug product name should be displayed as shown below:

Varubi
(rolapitant) tablets
*90 mg**
**(Equivalent to 100 mg rolapitant hydrochloride)*

2. Revise the carton labels to include the following:

- Display total number of tablets per carton e.g. “2 tablets”
- The inactive ingredients should be listed
- Revise the storage statement as shown below:

Store at 20° to 25°C (68° to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]

- Provide copies of immediate container and carton labels for all configurations you plan to market.

3. Immediate container and carton labels:

- Submit copies of labels for all different types of drug product packages you intend to market.

C. Regarding PI

“Highlights” Section

- Proprietary and established name, dosage form and dosage administration should be as follows:

Proprietary name (rolapitant) tablets, for oral use

- “Dosage forms and strengths” should be as follows:

Tablets: 90 mg rolapitant

(b) (4)

#3. Dosage Forms and Strength

- The rolapitant tablet strength should be 90 mg

-

(b) (4)

#11 Description

- Proprietary and established name, dosage form and strength should be as follows:

Proprietary name (rolapitant) tablets, 90 mg

- An equivalency statement should be added as shown below:

Equivalent to 100 mg rolapitant hydrochloride

- The chemical name and empirical formula should be corrected as follows:

(5S,8S)-8-[[[(1R)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-methyl]-8-phenyl-1,7-diazaspiro[4.5]decan-2-one hydrochloride monohydrate

#16 How supplied/storage and Handling

- The rolapitant table strength should be 90 mg
- Include description of tablets e.g. shape, color etc.
- Provide NDC numbers, number of tablets per blister pack, number of blister packs per carton for all different type of drug packages you intend to market
- The storage conditions should be as follows:

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted

(b) (4) 15°C to 30°C (59°F to 86°F)[see USP Controlled Room Temperature]

III. Attachments

A. Facility

OVERALL RECOMMENDATION: “ <u>Approve</u> ” Recommendation entered into Panorama on 4/15/2015 with a re-evaluation date of 4/26/2016.				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION (b) (4)
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION (b) (4)

B. Lifecycle Knowledge Management

a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking*	Justification	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments**
(b) (4) Impurities					
Mutagenic impurities					
Heavy Metal impurities					

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Rankin g*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
(b) (4)					

(b) (4)

