# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208399Orig1s000

# PRODUCT QUALITY REVIEW(S)

**Memorandum**

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

**Date:** **October 19, 2017**
**From:** **Hitesh Shroff, Ph.D.**
**Application Technical Lead, Branch V**
**Division of New Drug Products II Office**
**of New Drug Products**

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

**To:** **OPQ Review #2 of NDA 208399**

**Subject: Final Recommendation for NDA 208399**

At the time when the OPQ Review #2 was completed on September 26, 2017, it had noted the following pending issues:

- The label/labeling issues were not resolved.

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

Tesaro submitted revised Package Insert on October 18, 2017 and container/carton labels on October 19, 2017. The CMC sections of the labels and labeling were reviewed and found acceptable. (see Labeling Memorandum)

Tesaro has submitted updated MBR on September 28, 2017 in response to the IR from Office of Process and Facilities. The updated MBR is deemed adequate from process perspective. (see Process Memorandum).

**Recommendation:**
This NDA is now recommended for Approval from the OPQ perspective.

**Application Technical Lead's Assessment and Signature**

The NDA is recommended for Approval from quality perspective.

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

Hitesh N. Shroff -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2017.10.20 10:47:50 -04'00'

# MEMO TO FILE

**NDA:** 208399

**From:** Yuesheng Ye, Ph.D.
Process Reviewer, Branch VIII, DPA III, OPF

**Through:** Nallaperumal Chidambaram, Ph.D.
Branch Chief, Branch VIII, DPA III, OPF

**Date:** 10/02/2017

**SUBJECT:** MEMORANDUM to NDA 208399 Process Review

## Master Batch Record

The Agency issued five process related Information Requests (IRs) dated August 24, 2017. Information request #2 recommended the applicant to tighten the proposed (b) (4) (b) (4) with the rate supported by the manufacturing data as well as provide an updated Master Batch Record (MBR). The applicant in response dated September 7, 2017, agreed to a tighter control of (b) (4) that is supported by data, however, they said that the official MBR was undergoing revision through their manufacturing site quality system and would be submitted to the Agency by October 02, 2017.

This memo is an evaluation of the updated MBR submitted on September 28, 2017. We find the updated MBR adequate.

## Recommendation

Acceptable from the process point of view

Yuesheng Ye, Ph.D.
Process Reviewer, Branch VIII, DPA III, OPF

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuesheng Ye -S, 0.9.2342.19200300.100.1.1=2001306205
Date: 2017.10.02 16:13:12 -04'00'

Nallaperumal Chidambaram, Ph.D.
Branch Chief, Branch VIII, DPA III, OPF

Nallaperumal Chidambaram -S Digitally signed by Nallaperumal Chidambaram -S
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**Recommendation:** As of this review, this 505 (b)(2) NDA resubmission is ***Not Ready*** for approval in its present form per 21 CFR 314.125(b)(6).

# NDA 208399
# OPQ Review # 2

| | |
|---|---|
| Drug Name/Dosage Form | Varubi (rolapitant) injectable emulsion |
| Strength | 166.5 mg/92.5 mL (1.8 mg/mL) of rolapitant in a single-dose vial |
| Route of Administration | Intravenous injection |
| Rx/OTC Dispensed | Rx |
| Applicant | Tesaro Inc., Waltham, MA |
| US agent, if applicable | N/A |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|---|---|---|
| Amendment - Resubmission | 04/25/2017 | OPQ |
| Amendment | 06/02/2017 | OPF |
| Amendment | 07/13/2017 | ONDP, OPF |
| Amendment | 07/20/2017 | ONDP, OPF |
| Amendment | 08/09/2017 | ONDP |
| Amendment | 08/25/207 | ONDP |
| Amendment | 09/07/2017 | OPF |
| Amendment | 09/13/2017 | OPF |
| Amendment | 09/18/2017 | ONDP |
| Amendment | 09/20/2017 | OPF |
| Amendment | 09/25/2017 | ONDP |

## Quality Review Team

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|---|---|---|
| Drug Substance | Debasis Ghosh | CDER/OPQ/ONDP/ DNDAPI/NDBII |
| Drug Product | Hitesh Shroff | CDER/OPQ/ONDP/ DNDPII/NDPBV |
| Process | Yuesheng Ye | CDER/OPQ/OPF/ DPAI/PABI |
| Microbiology | Eric Adeeku | CDER/OPQ/ OPF/DMA/MABI |
| Facility | Vidya Pai | CDER/OPQ/OPF/DIA/IABIII |
| Biopharmaceutics | Hansong Chen | CDER/OPQ/ONDP/ DB/BBII |
| Regulatory Project Manager | Mary Chung | CDER/OND/ODEIII/ DGIEP |
| Application Technical Lead | Hitesh Shroff | CDER/OPQ/ONDP/ DNDPII/NDPBV |
| Laboratory (OTR) | N/A | N/A |
| ORA Lead | Paul Perdue Jr. | ORA/OO/OMPTO/ DMPTPO/MDTP |
| Environmental Analysis (EA) | Hitesh Shroff | CDER/OPQ/ONDP/ DNDPII/NDPBV |

# Quality Review Data Sheet

## 1. RELATED/SUPPORTING DOCUMENTS

**A. DMFs: (see Review #1)**
**Other Documents:** *IND, RLD, or sister applications* **(see Review #1)**

| | | |
|---|---|---|
| | | |
| | | |
| | | |

## 2. CONSULTS: None

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

# Executive Summary

## I. Recommendations and Conclusion on Approvability

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

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

Biopharmaceutics issues regarding in-vitro release method have been adequately resolved.

The applicant has adequately addressed the durg product manufacturing process related deficiencies described in the Complete Response letter dated Januarry 11, 2017.

The label/labeling issues have ***not*** been completely resolved yet.

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

Therefore, from the OPQ perspective, this NDA is deemed ***not ready*** for Approval until label/labeling issues are satisfactorily resolved .

## II. Summary of Quality Assessments

- This NDA was originally submitted on March 11, 2016, and it was not recommended for approval from OPQ perspective because of the following deficiencies (see OPQ review dated December 09, 2016). A Complete Response (CR) letter was issued on January 11, 2017. Office of Process and Facilities made a final overall "Unacceptable" recommendation for the facilities involved in this application
- Biopharmaceutics issues regarding lack of an in-vitro release method for assessing the drug product quality when changes in manufacturing process, globule size and reagents are slightly modified or changed were not adequately resolved.
- The label/labeling issues were not completely resolved.

On April 25, 2017 Tesaro submitted an amendment to the CR letter that included the following:

- Provided in-vitro drug release method and method validation results
- Removed unacceptable manufacturing sites for this NDA and market the drug product manufactured at [redacted] (b) (4) site only
- Provided batch analysis data of multiple drug product batches packaged in [redacted] (b) (4) glass vials
- Addressed the drug product manufacturing process related deficiencies

Tesaro's response to the deficiencies described in the CR letter and subsequent amendments are reviewed in this OPQ quality review.

A. **Product Overview**

Rolapitant injectable emulsion is supplied as a sterile, translucent, white homogeneous emulsion in a glass vials. Each vial delivers 166.5 mg rolapitant (equivalent to 185 mg rolapitant hydrochloride) in 92.5 mL emulsion.

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | Rolapitant injectable emulsion is indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomitin. |
| **Duration of Treatment** | As needed |
| **Maximum Daily Dose** | Recommended daily dosage is 166.5 mg rolapitant administered as an intravenous infusion over 30 minutes within 2 hours prior to the initiation of chemotherapy |
| **Alternative Methods of Administration** | **N/A** |

B. **Quality Assessment Overview**

**Drug Substance:**
Approval from the Drug Substance perspective **(see OPQ Review #1)**

**Drug Product:**
Approval from the Drug Product perspective **(see OPQ Review #1)**

**Biopharmaceutics**
The proposed in vitro drug release method (IVDR) and acceptance criteria in this resubmission were reviewed by the Biopharmaceutics reviewer, Dr. Hansong Chen, and deemed acceptable. The biowaiver request from Tesaro was accepted and an additional *in vivo* bioequivalence (BE) bridging study is not needed from Biopharmaceutics perspective. From Biopharmaceutics perspective, this application is recommended for approval (see Biopharmaceutics Chapter in this review), however,a comment regarding the IVDR method should be conveyed to Tesaro (see **Attachement IV**).

On September 25, 2017, The applicant revised the dissolution acceptance criteria per Biopharmaceutics' recommendation. (see **Attachement V)**

**Facilities and Process:**
All manufacturing and testing facilities in connection with this NDA were now found **Acceptable**. (see Facilities Chapter of this Review)

**Labels and Labeling:**
The labels and labeling issues have **not** been satisfactorily resolved yet. (see the **Attachment III**).

**Special Product Quality Labeling Recommendations:** None

**Final Risk Assessment (see Attachment I)**

## OVERALL ASSESSMENT AND SIGNATURES:

From the OPQ perspective, this NDA is ***not*** deemed ready for Approval in its present form per 21 CFR 314.125(b)(6) until the labeling/label issues are satisfactorilty resolved .

## *Application Technical Lead Name and Date:*

Hitesh Shroff
Division of New Products II, Branch V
September 26, 2017

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
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# BIOPHARMACEUTICS

**Product Background:**

**NDA/ANDA:** NDA 208399 resubmission

**Drug Product Name / Strength:** Varubi (rolapitant) injectable emulsion 185 mg/92.5 mL (b) (4) mg/mL)

**Route of Administration:** IV injection

**Applicant Name:** Tesaro, Inc.

***Review Summary:***

Tesaro, Inc. developed Varubi (rolapitant hydrochloride) 100 mg oral tablets, which was approved by the FDA under NDA 206500 on 9/1/2015. It is indicated for prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

Tesaro further developed Varubi (rolapitant hydrochloride) injectable emulsion 185 mg /92.5 mL (b) (4)) and submitted the original submission, NDA 208399, to the Agency on 3/11/2016 to seek approval through a 505 b (1) pathway referencing NDA 206500 (100 mg oral tablet).

The Applicant initially did not propose in vitro drug release (IVDR) testing method as a quality control for release and stability testing for the proposed drug product (DP). Instead, they proposed a (b) (4) as for quality control metric and expressed technical difficulties/challenges on further development on IVDR method. However, the correlation between the (b) (4) and the in vitro release is not clearly demonstrated.

Per request by the Agency, the Applicant started to develop an IVDR method and submitted preliminary results for review on 11/03/2016. The above results included in the summary report were considered incomplete, and therefore, NDA 208399 is too premature for approval after the first review cycle.

Furthermore, the Applicant initially proposed (b) (4) (b) (4) (b) (4) as the manufacturing site for injectable rolapitant emulsion DP; however, the above site failed the FDA inspection. The Applicant then proposed an alternative manufacturing site, (b) (4) in (b) (4) No bridging information was included to support two manufacturing sites.

On 1/11/2017, the FDA issued a CR letter to NDA 208399 original submission. Please see **"Key Outstanding Issues from Last Cycle"** section below in this review for details. For the

needed bridging/comparability between the two manufacturing sites, please see "**Clinical Pharmacology**" section in the CR letter for details.

Several Teleconferences were made between the Applicant and the Division of Biopharmaceutics (DB) for discussions on the IVDR method development prior to NDA resubmission. On 4/25/2017, the Applicant resubmitted NDA 208399 to the Agency to address the CR deficiencies.

In this NDA resubmission, the Biopharmaceutics review is focusing on the Applicant's responses to the Biopharmaceutics deficiencies, i.e., IVDR method development, IVDR method validation, in vitro release profile data, comparative IVDR profile assessment, proposed IVDR specification for quality control, and the biowaiver request for waiving a bridging BE study between the two manufacturing sites.

The proposed IVDR Method were reviewed and found to be acceptable. On 9/20/2017, based on an overall mean of all 7 batches including the pivotal biobatch No. 22901.001 from (b) (4), the Agency proposed the following IVDR acceptance criteria:
At 15 minutes: (b) (4)
At 60 minutes:
At 180 minutes: No less than (NLT) (b) (4)
On 9/25/2017, the Applicant accepted the above IVDR acceptance criteria.

The Applicant provided sufficient supporting data to bridge the products manufactured in (b) (4). The biowaiver request of the requirement for the submission of evidence of in vivo bioavailability or bioequivalence (BE/BA) is granted. Overall, the Applicant adequately addressed the Biopharmaceutics deficiencies included in the CR letter.

From the Biopharmaceutics perspective, this Reviewer recommends that NDA 208399 resubmission Varubi (rolapitant) injectable emulsion 185 mg/92.5 mL is ADEQUATE for approval. The following comment needs to be conveyed to the Applicant:

> This is NOT a Post-Approval Comment (PMC).
> Your proposed in-vitro drug release (IVDR) method is reviewed and found acceptable at this moment; (b) (4)
>
> It is highly recommended you look into the literature and the USP database for a faster and/or a better IVDR method. After you explore, test, validate, and update a newly proposed IVDR method, (b) (4) (b) (4) In the meantime, you can request meetings to discuss with the Agency the progress of your adventure. The Agency will be happy to discuss with you for the progress /improvement towards the new IVDR method development in the future for better quality control of your drug product.

**List Submissions being reviewed (table):**

| SUBMISSION(S) REVIEWED NDA 208399 resubmission | DOCUMENT DATE |
|---|---|
| 0042 | 4/25/2017 |
| 0044 | 6/2/2017 |
| 0045 | 7/13/2017 |
| 0046 | 7/20/2017 |
| 0047 | 8/9/2017 |
| 0048 | 8/25/2017 |
| 0053 | 9/25/2017 |

**Highlight Key Outstanding Issues from Last Cycle:**

In the 01/11/17 CR letter, the following Biopharmaceutics deficiencies were included:
Your submitted summary report for your proposed in vitro release method is considered inadequate to be acceptable. To respond to the complete response, you should continue to develop the method to address the following issues:

1. In Vitro Release Method development

(b) (4) [redacted]

2. Discriminatory capabilities of the in vitro release method
   - The proposed method shows discriminatory capabilities towards the changes in the composition of the formulation. However, you did not evaluate whether the proposed in vitro method can discriminate the changes in the manufacturing process.

3. Method validation:
   - You stated that (b) (4) [redacted] (b) (4) [redacted] You need to validate that above statement whether only released drug can permeate into (b) (4) [redacted]
   - You need to submit a method validation report for the in vitro release method instead of just a summary table for the validation of the analytical method.



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(b) (4)

[redacted]

**R Regional Information**

***Comparability Protocols***

**Reviewer's Assessment:**

***Post-Approval Commitments***

**Reviewer's Assessment:**

***Lifecycle Management Considerations***

***List of Deficiencies:***

*None.*

***Primary Biopharmaceutics Reviewer Name and Date:***

*Hansong Chen, Pharm.D., Ph.D., 6/15/2017, 9/5/2017*

*Biopharmaceutics reviewer*

*OPQ/ONDP/Division of Biopharmaceutics*

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

*I concur. 09/15/17*

***Tien-Mien Chen, Ph.D.***

***Acting Biopharm. Lead***

***DB/ONDP/OPQ/CDER/FDA***

*I concur. 09/26/17*

***Tapash Ghosh, Ph.D.***

***Biopharm, Branch Chief***

***DB/ONDP/OPQ/CDER/FDA***

Hansong Chen

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Tien Mien Chen

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Date: 9/21/2017 08:44:29AM
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Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 9/26/2017 12:35:31PM
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**Recommendation: As of this review, this 505 (b)(2) NDA is Not Recommended for Approval in its present form per *21 CFR 314.125(b)(6) and (13).***

# NDA 208399
# Review 1

| | |
|---|---|
| Drug Name/Dosage Form | Varubi (rolapitant) injectable emulsion |
| Strength | 166.5 mg/92.5 mL (1.8 mg/mL) of rolapitant in a single-dose vial |
| Route of Administration | Intravenous injection |
| Rx/OTC Dispensed | Rx |
| Applicant | Tesaro Inc., Waltham, MA |
| US agent, if applicable | N/A |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|---|---|---|
| Original | 03/11/2016 | OPQ |
| Amendment | 04/12/2016 | OPF |
| Amendment | 04/18/2016 | ONDP |
| Amendment | 06/13/2016 | ONDP |
| Amendment | 05/27/2016 | OPF |
| Amendment | 06/13/2016 | OPF |
| Amendment | 06/24/2016 | ONDP |
| Amendment | 07/22/2016 | OPF |
| Amendment | 07/29/2016 | ONDP |
| Amendment | 08/31/2016 | ONDP/OPF |
| Amendment | 09/09/2016 | ONDP |
| Amendment | 09/29/2016 | ONDP |
| Amendment | 10/24/2016 | ONDP |
| Amendment | 10/27/2016 | ONDP/OPF |
| Amendment | 11/07/2016 | ONDP |
| Amendment | 11/17/2016 | ONDP |
| Amendment | 11/18/2016 | OPF |
| Amendment | 11/21/2016 | OPF/DMA/MABI |

# QUALITY ASSESSMENT

## Quality Review Team

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|---|---|---|
| Drug Substance | Debasis Ghosh | CDER/OPQ/ONDP/ DNDAPI/NDBII |
| Drug Product | Hitesh Shroff | CDER/OPQ/ONDP/ DNDPII/NDPBV |
| Process | Yuesheng Ye | CDER/OPQ/OPF/ DPAI/PABI |
| Microbiology | Eric Adeeku | CDER/OPQ/ OPF/DMA/MABI |
| Facility | Vidya Pai | CDER/OPQ/OPF/DIA/IABIII |
| Biopharmaceutics | Hansong Chen | CDER/OPQ/ONDP/ DB/BBII |
| Regulatory Business Process Manager | Mary Chung | CDER/OND/ODEIII/ DGIEP |
| Application Technical Lead | Hitesh Shroff | CDER/OPQ/ONDP/ DNDPII/NDPBV |
| Laboratory (OTR) | N/A | N/A |
| ORA Lead | Paul Perdue Jr. | ORA/OO/OMPTO/ DMPTPO/MDTP |
| Environmental Analysis (EA) | Hitesh Shroff | CDER/OPQ/ONDP/ DNDPII/NDPBV |

# Quality Review Data Sheet

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | STATUS[1] | COMMENTS |
|---|---|---|---|---|---|
| (b) (4) | IV | (b) (4) | (b) (4) | N/A | N/A |
| | III | | | N/A | N/A |
| | V | | | N/A | N/A |
| | II | | | N/A | N/A |
| | III | | | N/A | N/A |
| | V | | | N/A | N/A |
| | V | | | N/A | N/A |
| | V | | | N/A | N/A |
| (b) (4) | V | (b) (4) | (b) (4) | N/A | N/A |
| | II | | | N/A | N/A |

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 | Rolapitant capsules |
| IND | 117307 | Rolapitant IV injection |
| NDA | 206500 | Rolapitant tablets |

**2. CONSULTS: None**

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

# Executive Summary

## I. Recommendations and Conclusion on Approvability

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

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

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

Biopharmaceutics issues regarding in-vitro release method have ***not*** been adequately resolved.

The label/labeling issues have ***not*** been completely resolved as of this review.

Therefore, from the OPQ perspective, this NDA is ***not*** recommended for approval at this time in its present form per 21 CFR 314.125(b)(6) and (13) until the above issues are satisfactorily resolved. **(see the Attachment II)**

## II. Summary of Quality Assessments

### A. Product Overview

Rolapitant injectable emulsion is supplied as a sterile, translucent, white homogeneous emulsion in a (b) (4) vials. Each vial delivers 166.5 mg rolapitant (equivalent to 185 mg rolapitant hydrochloride) in 92.5 mL emulsion.

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | Rolapitant injectable emulsion is indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomitin. |
| **Duration of Treatment** | As needed |
| **Maximum Daily Dose** | Recommended daily dosage is 166.5 mg rolapitant administered as an intravenous infusion over 30 minutes within 2 hours prior to the initiation of chemotherapy |
| **Alternative Methods of Administration** | **N/A** |

## Quality Assessment Overview

### Drug Substance:

(b) (4)

[redacted]

(b) (4)

**Drug Product:**

(b) (4)

(b) (4) The specification is deemed adequate per Drug Product reviewer, Dr. Hitesh Shroff (see the drug product review).

On the basis of the satisfactory stability data of drug product packaged in vials 12-month of expiration dating period from the date of the manufacture of the drug product including holding time is granted when stored at room temperature in the proposed container closure system.

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included.The claim was deemed acceptable.

**B. Special Product Quality Labeling Recommendations (NDA only)**
None

**Final Risk Assessment (see Attachment I)**

## OVERALL ASSESSMENT AND SIGNATURES:

From the OPQ perspective this NDA is ***not*** recommended for approval at this time in its present form per 21 CFR 314.125(b)(6) and (13).

***Application Technical Lead Name and Date:***
Hitesh Shroff
Division of New Products II, Branch V
December 8, 2016

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
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# LABELING

## R Regional Information

## 1.14 Labeling

***Labeling & Package Insert***

**1. Package Insert**

(a) "Highlights" Section

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use VARUBI safely and effectively. See full prescribing information for VARUBI.**
**VARUBI® (rolapitant) tablets, for oral use**
**VARUBI® (rolapitant) injectable emulsion, for intravenous use**
**Initial U.S. Approval: 2015**

**DOSAGE FORMS AND STRENGTHS**

- Injectable Emulsion: 166.5 mg/92.5 mL (1.8 mg/mL) of rolapitant in a single-dose vial (3)
- Tablets: 90 mg of rolapitant (3)

| Item | Information Provided in NDA |
|---|---|
| **Drug name (201.57(a)(2))** | |
| Proprietary name and established name | Proprietary and established names are described correctly as:<br><br>Varubi (rolapitant) tablets<br>Varubi ( rolapitant) injectable emulsion<br><br>**Satisfactory** |
| Dosage form, route of administration | Tablets, for oral use<br>Injectable emulsion, for intravenous use<br><br>**Satisfactory** |
| Controlled drug substance symbol (if applicable) | N/A |
| **Dosage Forms and Strengths (201.57(a)(8))** | |
| Whether the drug product is scored | This drug product is not scored |

This section is satisfactory.

(b) "Full Prescribing Information" Section

# 3: Dosage Forms and Strengths

**3. DOSAGE FORMS AND STRENGTHS**

VARUBI Injectable Emulsion: 166.5 mg 92.5 mL (1.8 mg mL) rolapitant as a translucent white homogenous emulsion in a single-dose vial

VARUBI Tablets: 90 mg rolapitant; film-coated capsule shaped blue tablets, debossed with T0101 on one side and 100 on the other side.

| Item | Information Provided in NDA |
|---|---|
| Available dosage forms | Injectable Emulsion and Tablets<br><br>The dosage forms are indicated properly.<br>**Satisfactory** |
| Strengths: in metric system | Injectable emulsion: 166.5 mg/92.5 mL (1.8 mg/mL) or rolapitant in a single-dose vial<br><br>Tablets: 90 mg of rolapitant<br><br>**Satisfactory** |
| Active moiety expression of strength with equivalence statement (if applicable) | The equivalency statement is not provided.<br><br>**Not Satisfactory** |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. | Tablets: Film coated capsule shaped, blue tablets, debossed with T0101 on one side and 100 on the other side.<br><br>Injectable Emulsion: A translucent white homogenous emulsion in a single-dose vial.<br><br>**Satisfactory** |

This section should be revised to include the equivalency statements as shown below:

Varubi Injectable Emulsion: 166.5 mg/92.5 mL (1.8 mg/mL) of rolapitant in a single-dose vial (equivalent to 185 mg of rolapitant hydrochloride).

Tablets: 90 mg of rolapitant (equivalent to 100 mg rolapitant hydrochloride)

#11: Description

**11. DESCRIPTION**

(b) (4)

[redacted]

(b) (4)

This section should be revised as follows:

- **Varubi Injectable Emulsion should be revised to Varubi (rolapitant) Injectable emulsion, and Varubi Tablets should be revised to Varubi (rolapitant) Tablets**

- The molecular formula should be displayed as "$C_{25}H_{26}F_6N_2O_2.HCl.H_2O$"

- The Varubi Injectable Emulsion description should include the pH of the emulsion (7.0 – 8.0).

## #16: How Supplied/Storage and Handling

**16 HOW SUPPLIED/STORAGE AND HANDLING**

VARUBI Injectable Emulsion

VARUBI Injectable Emulsion is supplied as a sterile, translucent white homogenous emulsion in a stoppered vial. Each vial delivers 166.5 mg/92.5 mL (1.8 mg/mL) rolapitant:

NDC 69656-102-96 A single-dose vial

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

Do not freeze.

VARUBI tablets

VARUBI is available as film-coated, capsule shaped, blue tablets, debossed with T0101 on one side and 100 on the other side. Each tablet contains 90 mg rolapitant. VARUBI tablets are packaged in an Aclar blister shell with aluminum foil backing and supplied as follows:

NDC 69656-101-02 A single dose package (2 tablets as one set of twinned blisters)

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

| Item | Information Provided in NDA |
|---|---|
| Strength of dosage form | Injectable Emulsion: 166.5 mg/92.5 mL (1.8 mg/mL)<br><br>Tablets: 90 mg<br><br>The established names should be revised as stated for the Description section.<br><br>Strengths and dosage forms are indicated properly.<br><br>**Not Satisfactory** |
| Available units (e.g., bottles of 100 tablets) | A single dose vial of injectable emulsion and a single dose package (2 tablets as one set of twinned blisters)<br><br>**Satisfactory** |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | Injectable Emulsion: Sterile, translucent white homogenous emulsion in a stoppered vial.<br><br>Tablets: Film-coated, capsule shaped, blue tablets, debossed with T0101 on one side and 100 on the other side.<br><br>**Satisfactory** |
| Special handling (e.g., protect from light) | Do not freeze. |
| Storage conditions | Injectable Emulsion: Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [See USP Controlled Room Temperature]. Do not freeze.<br><br>Tablets: Store at 20°C - 25°C (68°F - 77°F); |

| | |
|---|---|
| | excursions permitted to 15°C - 30°C (59°F - 86°F) [See USP Controlled Room Temperature].<br><br>**Satisfactory** |
| Manufacturer/distributor name (21 CFR 201.1(h)(5)) | Tesaro Inc., 1000 Winter Street, #3300, Waltham, MA 02451<br><br>**Satisfactory** |

The established names should be correctly expressed This **section is satisfactory.**

### 2. *Immediate Container Label*

(b) (4)

| Item | Information Provided in NDA |
|---|---|
| Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)) | The drug product name is not presented correctly.<br><br>**Not Satisfactory** |
| Dosage strength | Displayed as 166.5 mg/92.5 mL (1.8 mg/mL)<br><br>**Satisfactory** |
| Net contents | Not displayed.<br><br>**Not Satisfactory** |
| "Rx only" displayed prominently on the main panel | Displayed.<br><br>**Satisfactory** |
| NDC number (21 CFR 207.35(b)(3)(i)) | (b) (4) [redacted]<br><br>**Not Satisfactory** |
| Lot number and expiration date (21 CFR 201.17) | Displayed correctly.<br><br>**Satisfactory** |
| Storage conditions | Displayed correctly.<br><br>**Satisfactory** |
| Bar code (21CFR 201.25) | Not displayed.<br><br>**Not Satisfactory** |
| Name of manufacturer/distributor | Displayed correctly.<br><br>**Satisfactory** |
| And others, if space is available | N/A |

This section should be revised as follows:

- The drug product name should be displayed as shown below:
  Varubi (rolapitant) injectable emulsion
- The net content of the vial should be displayed as "Net Content: 92.5 mL"
- The NDC number should be the same on all labeling.
- The bar code is required on the immediate container label per 21 CFR 201.25.

3. *Carton Labelin*

(b) (4)

| Item | Information Provided in NDA |
|---|---|
| Proprietary name, established name (font size, prominence) | The drug product name is not presented correctly.<br><br>**Not Satisfactory** |
| Dosage strength | Displayed as 166.5 mg/92.5 mL (1.8 mg/mL)<br><br>**Satisfactory** |
| Net quantity of dosage form | Not displayed.<br><br>**Not Satisfactory** |
| "Rx only" displayed prominently on the main panel | Displayed.<br><br>**Satisfactory** |
| Lot number and expiration date | Displayed correctly.<br><br>**Satisfactory** |
| Storage conditions | Displayed correctly.<br><br>**Satisfactory** |
| Bar code (21CFR 201.25) | Displayed.<br><br>**Satisfactory** |
| NDC number (21 CFR 207.35(b)(3)(i)) | (b) (4)<br><br>**Not Satisfactory** |
| Manufacturer/distributor's name | Displayed correctly.<br><br>**Satisfactory** |
| Quantitative ingredient information (injectables) | Displayed Correctly.<br><br>**Satisfactory** |
| Statement of being sterile (if applicable) | Displayed.<br><br>**Satisfactory** |
| "See package insert for dosage information" | Not displayed.<br><br>**Not Satisfactory** |
| "Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs) | Not displayed.<br><br>**Satisfactory** |

This section should be revised as follows:

- The drug product name should be displayed as shown below:
  Varubi (rolapitant) injectable emulsion
- The net content of the vial should be displayed as "Net Content: 92.5 mL"
- The NDC number should be the same on all labeling.
- The bar code is required on the immediate container label per 21 CFR 201.25.
- Display the following statement:
  See package insert for dosage information

**Reviewer's Assessment: Not Adequate**

The proposed labeling is not adequate in the present form.

The following sections in the package insert need revision.

- The Sec. #3 Dosage Forms and Strengths did not include equivalency statements.
- Sec. #11 Description the pH of the injectable emulsion should be included and the API molecular formula should be displayed properly.

The container and carton labels should be revised to include the following information.

- Bar code, net content and dosage information statement
- Same NDC numbers on labeling

***List of Deficiencies:***

**Regarding Label/Labeling**

**PI**

#3 Dosage Forms and Strength

- Varubi Injectable Emulsion: 166.5 mg/92.5 mL (1.8 mg/mL) of rolapitant in a single-dose vial (equivalent to 185 mg of rolapitant hydrochloride).
- Tablets: 90 mg of rolapitant (equivalent to 100 mg rolapitant hydrochloride)

#11 Description

- The molecular formula should be displayed as "$C_{25}H_{26}F_6N_2O_2.HCl.H_2O$"
- The Varubi Injectable Emulsion description should include the pH of the emulsion (7.0 – 8.0).

Immediate Container and Carton Labels

- The drug product name should be displayed as shown below:
  Varubi (rolapitant) injectable emulsion
- The net content of the vial should be displayed as "Net Content: 92.5 mL"
- The NDC number should be the same on all labeling.
- The bar code is required on the immediate container label per 21 CFR 201.25.

Carton Labels

- Display the following statement:
  See package insert for dosage information

## QUALITY ASSESSMENT

***Overall Assessment and Recommendation: Not Adequate***

The package insert, container and carton labels do not contain required information. They should be revised before approval of this application.

***Primary Labeling Reviewer Name and Date:***

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

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

I agree with Dr. Shroff's assessment of the labeling/labels and concur with his recommendation that this application is not ready for approval until the issues on the labeling/labels are satisfactorily resolved.

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

Moo Jhong Rhee

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Hitesh Shroff

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# BIOPHARMACEUTICS

**Product Background:**

**NDA/ANDA:** NDA 208399

**Drug Product Name / Strength:** Varubi (rolapitant) injectable emulsion 185 mg/92.5 mL

**Route of Administration:** IV injection

**Applicant Name:** Tesaro, Inc.

***Review Summary:***

Tesaro, Inc. developed Varubi (rolapitant hydrochloride) 100 mg oral tablets, which was approved by the FDA under NDA 206500 on 9/1/2015. It is indicated for prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

In this submission, Tesaro proposed Varubi (rolapitant hydrochloride) injectable emulsion (b) (4) (b) (4) and seeks approval through a 505 b (2) pathway referencing NDA 206500 (100 mg oral tablet).

The Applicant initially proposed (b) (4) instead of in vitro release method as a quality control metric and expressed technical difficulty/challenge on further development on in vitro release method. However, the correlation between (b) (4) and the in vitro release is not clearly demonstrated. Per request by the Agency, the Applicant started to develop an in vitro drug release method. The proposed in vitro release method development "summary" was just submitted on 11/23/16, which is too close to the PDUFA goal date (01/11/17).

From the Biopharmaceutics perspective, NDA 208399 for the proposed Varubi (rolapitant hydrochloride) injectable emulsion 185 mg/92.5 mL is NOT adequate for approval in this review cycle. The in vitro release method "summary" submitted on 11/23/16, however, was considered incomplete in terms of method development and its full validation reports. Furthermore, the Applicant has not adequately addressed the Biopharmaceutics Information Requests (IRs). Therefore, a CR is recommended.

As a result, the Clinpharm's request on employing this in vitro release method to assess the biowaiver between the two manufacturing sites is considered too premature. Therefore, it could not be used for this purpose at this moment.

The Applicant should continue to develop and validate the in vitro release method. Upon resubmission, the Applicant should provide complete in vitro release method development and

validation reports and fully address the Biopharmaceutics deficiencies related to the in vitro release method.
Finally, the Biopharmaceutics deficiencies need to be conveyed to the Applicant in the CR letter and to be address adequately in the resubmission of this NDA.

**List Submissions being reviewed (table):**

Application 208399 - Sequence 0001 - 0001 (1) 03/11/2016 ORIG-1 /Multiple Categories/Subcategories

| Module | Content |
|---|---|
| 3.2.P.1 | Description and Composition of the Drug Product |
| 3.2.P.5.1 | Specifications |
| 3.2.P.5.2 | Analytical procedures |

Application 208399 - Sequence 0009 - 0009 (9) 06/13/2016 ORIG-1 /Multiple Categories/Subcategories

Application 208399 - Sequence 0017 - 0017 (17) 07/22/2016 ORIG-1 /Quality/Response To Information Request

Application 208399 - Sequence 0026 - 0026 (26) 09/01/2016 ORIG-1 /Quality/Response To Information Request

Application 208399 - Sequence 0034 - 0034 (34) 11/03/2016 ORIG-1 /Quality/Response To Information Request

Application 208399 - Sequence 0040 - 0040 (40) 11/23/2016 ORIG-1 /Clinical Pharmacology/Response To Information Request

**Highlight Key Outstanding Issues from Last Cycle:**

**Concise Description Outstanding Issues Remaining:**

The Applicant has not successfully developed an acceptable in vitro release method as a quality control tool.

***BCS Designation***

**Reviewer's Assessment:** The Applicant reported that it is a BCS II drug, which has poor solubility and high permeability.

**Solubility:** The solubility of rolapitant HCl in aqueous solution is pH dependent.

Table 1. Solubility of Rolapitant Hydrochloride in Water

| pH | Solubility at Room Temperature (mg/mL) | Solubility at 37 °C (mg/mL) |
|---|---|---|
| 2.0 | 0.44[a] | 0.71[a] |
| 4.0 | 0.81 | 0.83 |
| 6.0 | 0.030 | 0.028 (at pH = 5.9) |
| 6.9 | 0.0072 | 0.012 |
| 7.4 | 0.006 | 0.010 at pH = 7.5) |

[a] Reduced solubility due to common ion effect of hydrochloric acid used for pH adjustment

**Permeability:** not reported.

**Dissolution:** An in vitro release method was proposed; however, the Applicant should continue to develop to make it acceptable.

***Dissolution Method and Acceptance Criteria***

**Reviewer's Assessment:**

Initially, the Applicant proposed (b) (4) instead of an in vitro release method for its proposed product's specification. The Agency expressed concerns that an in vitro release method is needed for quality control purposes. An IR for an in vitro release method development was included in the 74-Day letter. During the Biopharm review, three IRs were sent out and three T-cons were held with the Applicant.

However, in the T-con dated 10/4/2016, the Division of Biopharmaceutics allowed the Applicant to continue to develop an in vitro release method with discriminatory power under the post-approval commitment (PMC), if the NDA is presumably deemed approval.

Three Biopharmaceutics IRs had been communicated to the Applicant as stated below.

**1. Information request (IR) 1**

On 5/20/2016, the FDA sent the first Biopharmaceutics IR to the Applicant. On 6/13/2016, the Applicant responded to the IR. The following are the IR, the Applicant's Response, and Reviewer's comment.

**IR 1**

An in vitro release method needs to be developed for your proposed drug product, rolapitant in an emulsion dosage form, for drug product quality control purposes, i.e., drug performance and



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(b) (4)

## R Regional Information

***Comparability Protocols***

**Reviewer's Assessment:**

***Post-Approval Commitments***

**Reviewer's Assessment:**

***Lifecycle Management Considerations***

***List of Deficiencies:***

*The following information requests need to be conveyed to the Applicant:*

Your submitted summary report for your proposed in vitro release method is considered inadequate to be acceptable. To respond to the complete response, you should continue to develop the method to address the following issues:

1. In Vitro Release Method development

(b) (4)

(b) (4) Submit the complete in vitro release method development report to the Agency for review.

2. Discriminatory capabilities of the in vitro release method
   - The proposed method shows discriminatory capabilities towards the changes in the composition of the formulation. However, you did not evaluate whether the proposed in vitro method can discriminate the changes in the manufacturing process.

3. Method validation:
   - You stated that (b) (4) (b) (4) You need to validate that above statement whether only released drug can permeate into (b) (4)
   - You need to submit a method validation report for the in vitro release method instead of just a summary table for the validation of the analytical method.
   - You need to validate intermediate precision and robustness.

4. In vitro release data and specification
   - The Applicant did not report the complete in vitro release data (individual, mean, SD, RSD, mean profile) for other batches manufactured in (b) (4) Bathes 22903.002 and 22903.003) and (b) (4) (Bathes D004007, D004065, and D004077).
   - Batch D003419 could not match any batch number reported in Module 3.2.P.5.4 Batch analyses. You should provide detailed batch information.
   - You should compare the in vitro release profile of each batch manufactured in (b) (4) with that of each batch manufactured in (b) (4), and submit the complete comparative data to the Agency for review.
   - You should propose a specification for the in vitro release method.

5. You need to provide a scientific rationale/justification for the following statement.

(b) (4)

6. You should provide rationale/justification as to why the release of free rolapitant reached only around (b)(4)% after 300 min and find out where the rest of (b)(4)% would be since the solution of API could reach more than (b)(4)% using the same in vitro release method.

7. You should continue to develop the in vitro release method and adequately address the Biopharmaceutics deficiencies related to the in vitro method development and validation reports and in vitro release data in the resubmission to the Agency for a thorough review.

***Primary Biopharmaceutics Reviewer Name and Date:***

***Hansong Chen, 11/30/2016, 12/2/2016, 12/04/16***

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

***I concur. 12/05/16***

***Tien-Mien Chen, Ph.D.***

***Acting Biopharm. Lead***

***DB/ONDP/OPQ/CDER/FDA***

Tien Mien Chen

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Hansong Chen

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# MICROBIOLOGY

**Product Background:**
Rolapitant 1.8 mg/mL injectable emulsion for intravenous infusion is supplied as a translucent white homogenous emulsion in a 100-mL vial. Each vial has a nominal volume of 92.5 mL, containing 185 mg of rolapitant hydrochloride (equivalent to (b) (4) ).

**NDA: 208399**

**Drug Product Name / Strength:** Rolapitant Hydrochloride / 1.8 mg/mL

**Route of Administration:** IV

**Applicant Name:** Tesaro, Inc.

**Manufacturing Site:**
(b) (4)

(b) (4)

(b) (4)
[1]Formerly known as

**Method of Sterilization:** (b) (4)

***Review Summary:***

The submission is **recommended** for approval on the basis of sterility assurance. No outstanding microbiology deficiencies remain. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

**List Submissions being reviewed (table):**

| Submit | Received | Review Request | Assigned to Reviewer |
|---|---|---|---|
| 08/31/2016 | 08/31/2016 | N/A | 11/07/2016 |
| 11/21/2016 | 11/21/2016 | N/A | 11/21/2016 |

**Highlight Key Outstanding Issues from Last Cycle:** None

**Concise Description Outstanding Issues Remaining:** None

**SUPPORTING/RELATED DOCUMENTS:**

(b) (4)

(b) (4)

**REMARKS:**
This is an electronic submission.
The goal date is 01/11/2017.

This NDA was tentatively approved for sterility assurance by DMA. However, the applicant has provided a gratuitous amendment for the use of an alternate manufacturing facility and is the subject of this review.

The deficiencies issued in the 11/16/2016 microbiology information request were responded to in the 11/21/2016 submission.

## P.1 Description of the Composition of the Drug Product

**Reviewer's Assessment:**

(section 3.2.P.1).

| Ingredient | Function | Concentration (g/97.9 mL) | Amount / unit (g) |
|---|---|---|---|
| Rolapitant hydrochloride, in house | API | (b) (4) | (b) (4) |
| Polyoxyl 15 Hydroxystearate, USP-NF | (b) (4) | | |
| Medium-chain Triglycerides (b) (4) (b) (4), USP-NF | | | |
| Soybean oil, USP-NF | | | |
| Sodium chloride, USP-NF | | | |
| Dibasic Sodium phosphate anhydrous, USP-NF | | | |
| Hydrochloric acid USP-NF | | | |
| Sodium hydroxide USP-NF | | | |
| Water for Injection, USP-NF | | | |

(b) (4)

(section 3.2.P.2; section 3.2.P.7).

| Component | Description | Manufacturer |
|---|---|---|
| Vials | (b) (4) | |
| Stoppers | | |
| Seals | | |

**Acceptable**

## P.2 Pharmaceutical Development

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Eric Adeeku

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Jesse Wells

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# Attachments:

## ATTACHMENT I: Risk Assessment

**Initial Risk Assessment for NDA 208339 Rolapitant Injectable Emulsion for Intravenous Use**

| Product Attribute / CQA | Factors that can impact the CQA | Risk Ranking | Risk Mitigation Approach | Risk Evaluation | LifeCycle consideration/ Comments (b) (4) |
|---|---|---|---|---|---|
| Emulsion Appearance | Emulsion separation, globules aggregation, (b) (4)<br><br>Manufacturing process | M to H | | | |
| Assay | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | L | | | |

| | | | |
|---|---|---|---|
| Sterility | •Process parameters<br>• Container/closure system | L | (b) (4) |
| Globule size | • Formulation<br>• Process parameters<br>• Scale/equipment<br>• Site | M to H | |

**ATTACHMENT II: List of Deficiencies for Complete Response**

**A. Regarding Biopharaceutics:**

1. In Vitro Release Method development

(b) (4)

2. Discriminatory capabilities of the in vitro release method
   - The proposed method shows discriminatory capabilities towards the changes in the composition of the formulation. However, you did not evaluate whether the proposed in vitro method can discriminate the changes in the manufacturing process.

3. Method validation:
   - You stated that (b) (4) (b) (4) You need to validate that above statement whether only released drug can permeate into (b) (4)
   - You need to submit a method validation report for the in vitro release method instead of just a summary table for the validation of the analytical method.
   - You need to validate intermediate precision and robustness.

4. In vitro release data and specification
   - The Applicant did not report the complete in vitro release data (individual, mean, SD, RSD, mean profile) for other batches manufactured in (b) (4) (Bathes 22903.002 and 22903.003) and (b) (4) (Bathes D004007, D004065, and D004077).
   - Batch D003419 could not match any batch number reported in Module 3.2.P.5.4 Batch analyses. You should provide detailed batch information.

- You should compare the in vitro release profile of each batch manufactured in (b) (4) with that of each batch manufactured in (b) (4) and submit the complete comparative data to the Agency for review.
- You should propose a specification for the in vitro release method.

5. You need to provide a scientific rationale/justification for the following statement. (b) (4)

6. You should provide rationale/justification as to why the release of free rolapitant reached only around (b) (4)% after 300 min and find out where the rest of (b) (4)% would be since the solution of API could reach more than (b) (4)% using the same in vitro release method.

7. You should continue to develop the in vitro release method and adequately address the Biopharmaceutics deficiencies related to the in vitro method development and validation reports and in vitro release data in the resubmission to the Agency for a thorough review.

**B. Regarding Facility Inspections:**

- During a recent inspection of (b) (4), drug product manufacturing facility for this NDA our field investigators observed objectionable conditions and conveyed that information to the representative of thefacility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

**C. Regarding Labeling/Labels:**

- The issues on labeling/labels have not been not finalized yet.

**Memorandum**

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

**Date:** **October 19, 2017**

**From:** **Hitesh Shroff, Ph.D.**
**Division of New Drug Products II**
**Office of New Drug Products**

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

**To:** **OPQ Review #2 of NDA 208399**

**Subject:** **Final Recommendation**

The OPQ review #2 has noted the following pending labeling issues:

**Regarding of the Container/Carton Labels:**

**Immediate Container Labels**

- List all inactive ingredients in alphabetical order
- Display the drug product strength as "166.5 mg/92.5 mL (1.8 mg/mL)" under the drug product title.

**Carton Labels**

- Display lot number and expiration date as "Lot:" and "Exp:"

And because of these deficiencies, in the OPQ Review #2, this NDA was not recommended for approval from the labeling perspective.

Tesaro submitted revised Package Insert on October 18, 2017 and container/carton labels on October 19, 2017. The CMC sections of the labels and labeling were reviewed and found acceptable. (see Attachment)

**Recommendation:**

This NDA is **now** recommended for approval from the labeling perspective.

## Attachment: Package Insert and Labels

## A. PI

HIGHLIGHTS OF PRESCRIBING INFORMATION

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use VARUBI safely and effectively. See full prescribing information for VARUBI.**

**VARUBI® (rolapitant) tablets, for oral use**
**VARUBI® (rolapitant) injectable emulsion, for intravenous use**
**Initial U.S. Approval: 2015**

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

- Tablets: 90 mg of rolapitant (3)
- Injectable emulsion: 166.5 mg/92.5 mL (1.8 mg/mL) of rolapitant in a single-dose vial (3)

FULL PRESCRIBING INFORMATION: CONTENTS
3 DOSAGE FORMS AND STRENGTHS

**3 DOSAGE FORMS AND STRENGTHS**

VARUBI tablets: 90 mg rolapitant; film-coated capsule shaped, blue tablets, debossed with T0101 on one side and 100 on the other side.

VARUBI injectable emulsion: 166.5 mg/92.5 mL (1.8 mg/mL) rolapitant as a sterile, translucent white homogeneous liquid with some opalescence in a single-dose vial.

## 11 DESCRIPTION

**11 DESCRIPTION**

VARUBI contains rolapitant, a substance P/neurokinin 1 (NK1) receptor antagonist. Rolapitant hydrochloride is 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. Its empirical formula is $C_{25}H_{26}F_6N_2O_2 \cdot HCl \cdot H_2O$, and its structural formula is:

rolapitant hydrochloride

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 has good solubility in common pharmaceutical solvents such as ethanol, propylene glycol and 40% hydroxypropyl beta-cyclodextrin.

VARUBI (rolapitant) Tablets
Each tablet contains 90 mg rolapitant (equivalent to 100 mg rolapitant hydrochloride) and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and pregelatinized starch. The tablets are coated in non-functional blue and clear coats. The tablet coating comprises the following inactive ingredients: FD&C Blue No. 2-Indigo Carmine Lake, polyethylene glycol, polysorbate 80, polyvinyl alcohol, talc, and titanium dioxide.

VARUBI (rolapitant) Injectable Emulsion
Each single-dose vial of 92.5 mL sterile emulsion for intravenous use contains 166.5 mg rolapitant (equivalent to 185 mg of rolapitant hydrochloride) and the following inactive ingredients: dibasic sodium phosphate, anhydrous (2.8 mg/mL), medium chain triglycerides (11 mg/mL), polyoxyl 15 hydroxystearate (44 mg/mL), sodium chloride (6.2 mg/mL), soybean oil (6.5 mg/mL), water for injection and may contain hydrochloric acid and/or sodium hydroxide to adjust pH to 7.0 to 8.0. VARUBI injectable emulsion is a sterile, translucent white liquid and has some opalescence.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

**16 HOW SUPPLIED/STORAGE AND HANDLING**

VARUBI Tablets

VARUBI tablets are available as film-coated, capsule shaped, blue tablets, debossed with T0101 on one side and 100 on the other side. Each tablet contains 90 mg rolapitant. VARUBI tablets are packaged in an Actar blister shell with aluminum foil backing and supplied as follows:

NDC 69656-101-02 A single dose package (2 tablets as one set of twinned blisters)

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

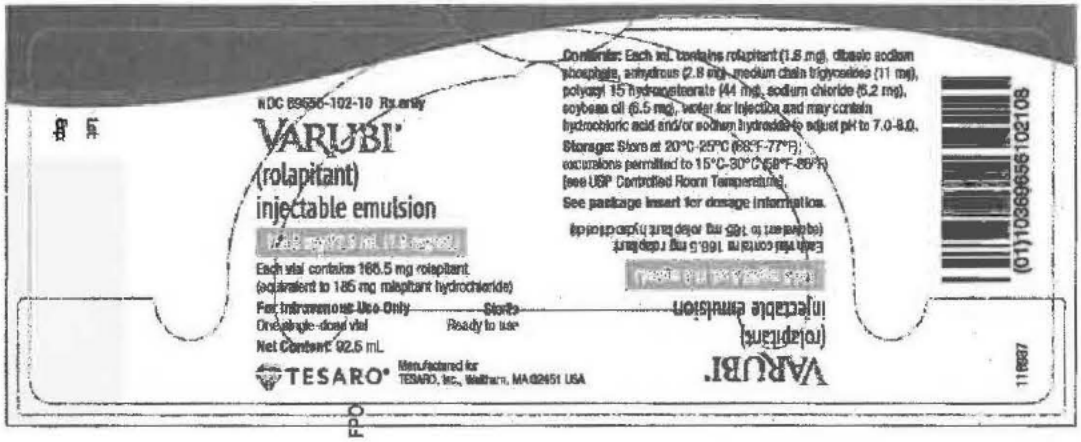
VARUBI Injectable Emulsion

VARUBI injectable emulsion is supplied as a sterile, translucent white homogeneous liquid that has some opalescence. Each stoppered vial delivers 166.5 mg/92.5 mL (1.8 mg/mL) rolapitant:

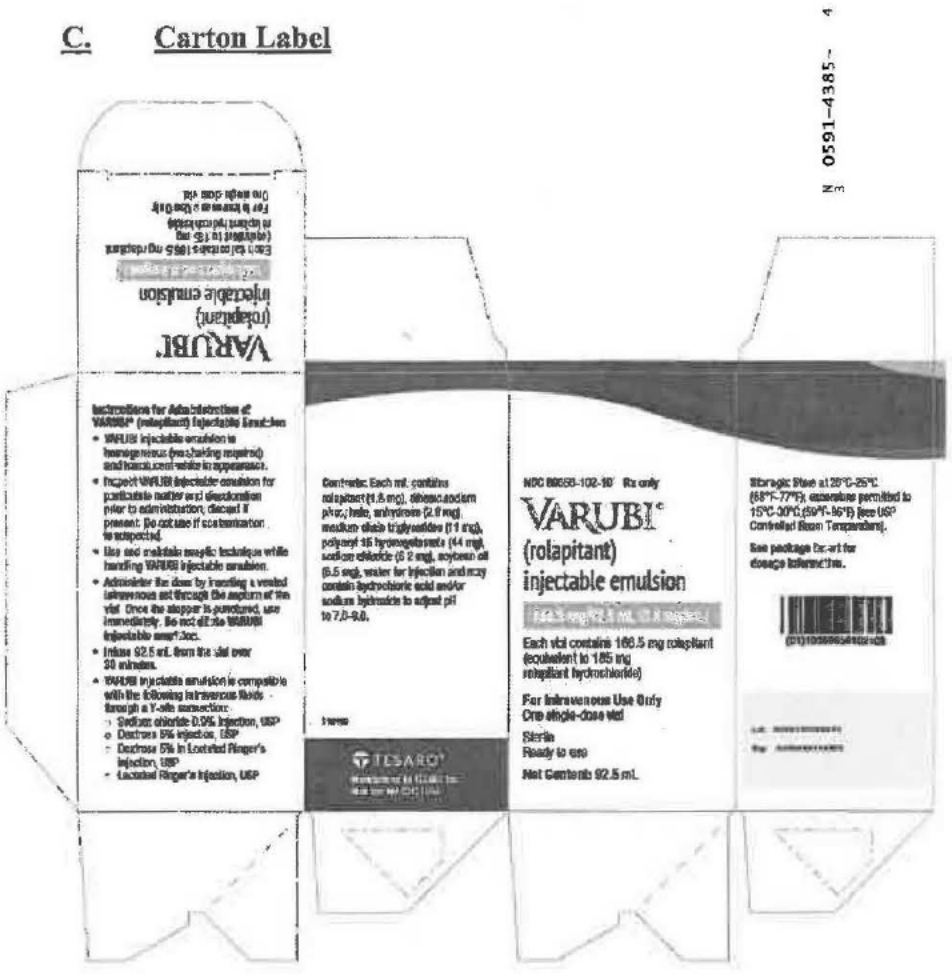
NDC 69656-102-10 One single-dose vial

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

## B. Container Label




## C. Carton Label



***Overall Assessment and Recommendation: Adequate***
The revised label and labeling submitted on October 18, 2017 and October 19, 2017 are satisfactory from ONDP perspective.

***Primary Labeling Reviewer Name and Date:***
Hitesh Shroff, Ph.D.
CMC Reviewer
Branch V, DNDP II/ONDP

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2017.10.20 10:15:41 -04'00'

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

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

Moojhong Rhee -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
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