

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208399Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208399 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Varubi Established/Proper Name: rolapitant Dosage Form: injection		Applicant: Tesaro, Inc. Agent for Applicant (if applicable):
RPM: Mary Chung		Division: Division of Gastroenterology and Inborn Errors Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>October 25, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☐ None CR, 1/11/2017
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 3
 (confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters

❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s): Approval, 10/25/17 Complete Response, 1/11/17

Labeling

❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	

• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included

• Original applicant-proposed labeling	☒ Included

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None

• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included

• Original applicant-proposed labeling	☒ Included

❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	

• Most-recent draft labeling	☒ Included

❖ Proprietary Name • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i>	Proprietary name granted: 7/21/17, 7/22/16 Proprietary name review: 7/18/17, 7/19/16

❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☐ None 10/20/17 DMEPA: ☐ None 9/25/17, 8/30/17, 12/7/16 DMPP/PLT (DRISK): ☐ None 9/25/17, 12/6/16 OPDP: ☐ None 9/21/17, 12/5/16 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None <i>see OPQ review 10/20/17, 9/26/17, 12/9/16</i> Other: ☐ None DPMH Maternal Health: 9/12/17, 12/1/16; DPMH Pediatric 9/21/17, 12/6/16

Administrative / Regulatory Documents

❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	5/5/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	☒ Completed (Do not include)

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>September 20, 2017</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	10/24/17, 10/20/17, 10/18/17, 10/16/17, 9/27/17, 9/26/17, 9/25/17, 9/20/17, 9/11/17, 9/5/17, 8/24/17, 7/10/17, 5/18/17, 11/15/16, 10/18/16, 9/22/16, 8/31/16, 8/29/16, 8/25/16, 8/4/16, 7/26/17, 7/25/16, 7/22/16, 7/14/16, 6/29/16, 5/24/16, 5/2/16, 4/25/16
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☐ N/A or no mtg 3/22/17
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 1/21/16 (sponsor withdrew meeting upon receipt of 1/21/16 prelim. comm.)
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 10/25/17, 1/11/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 10/23/17, 12/21/16
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 5 (4 PMRs, 1 PMC)
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	9/20/17, 12/1/16
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Pages 10-11 of 12/1/16 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☐ None DPMH Pediatric 9/21/17
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☐ N/A 12/7/16
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	☐ None 9/24/17, 12/7/16
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☐ None requested 8/19/16, 6/27/16
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	☐ None 9/14/17, 11/28/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	☒ None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	☐ None 10/20/17, 9/26/17, 12/9/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	9/26/17
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) <i>(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	☒ Acceptable 9/26/17 ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity <i>(Notify CDER OND IO)</i>
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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/s/

MARY H CHUNG
10/26/2017

Chung, Mary

From: Chung, Mary
Sent: Tuesday, October 24, 2017 6:30 PM
To: Seth Miller (smiller@tesarobio.com)
Cc: Chung, Mary
Subject: NDA 208399 rolapitant inj. emulsion- PI
Attachments: NDA 208399 rolapitant inj emuls FDA proposed PI annotated 10-24-17.pdf; NDA 208399 rolapitant inj emuls FDA proposed PI annotated 10-24-17.docx; NDA 208399 rolapitant inj emuls FDA proposed PI clean 10-24-17.pdf; NDA 208399 rolapitant inj emuls FDA proposed PI clean 10-24-17.docx

Hello Seth,

Reference is made to your April 25, 2017 resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion.

On October 20, 2017, we received your proposed labeling submission (PI) to this application, and have proposed revisions that are included as an enclosure (PI). We request that you resubmit labeling (PI) that addresses these issues to the NDA as soon as able or no later than 10:00 AM EST October 25, 2017.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0260. Thank you.

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

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/s/

MARY H CHUNG
10/24/2017

Chung, Mary

From: Chung, Mary
Sent: Friday, October 20, 2017 11:37 AM
To: Seth Miller (smiller@tesarobio.com)
Cc: Chung, Mary
Subject: NDA 208399 rolapitant inj. emulsion- PI
Attachments: NDA 208399 PI FDA proposed annotated 10-20-17.pdf; NDA 208399 PI FDA proposed annotated 10-20-17.docx; NDA 208399 PI FDA proposed clean 10-20-17.pdf; NDA 208399 PI FDA proposed clean 10-20-17.docx

Hello Seth,

Reference is made to your April 25, 2017 resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion.

On October 18, 2017, we received your proposed labeling submission (PI and PPI) to this application, and have proposed revisions that are included as an enclosure (PI). We request that you resubmit labeling (PI) that addresses these issues to the NDA by October 23, 2017.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
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Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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MARY H CHUNG
10/20/2017

From: Chung, Mary
Sent: Wednesday, October 18, 2017 4:05 PM
To: Seth Miller (smiller@tesarobio.com)
Cc: Chung, Mary
Subject: NDA 208399 rolapitant inj. emulsion- carton/container label

Hello Seth,

Reference is made to your April 25, 2017 resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion.

We have the following comments and recommendations for your proposed draft carton/container label submitted on October 16, 2017.

Please revise the equivalency statement on the container/carton labels as shown below:

Each vial contains 166.5 mg rolapitant
(equivalent to 185 mg rolapitant hydrochloride)

We request you submit your draft proposed carton/container label which addresses the above to the NDA October 19, 2017.

Regards,
Mary

Mary Chung, PharmD,
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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From: [Chung, Mary](#)
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 Varubi (rolapitant) inj. emulsion- PI PPI
Date: Monday, October 16, 2017 10:24:58 AM
Attachments: [NDA 208399 Varubi \(rolapitant\) inj emulsion PI FDA proposed annotated 10-16-17.pdf](#)
[NDA 208399 Varubi \(rolapitant\) inj emulsion PI FDA proposed annotated 10-16-17.docx](#)
[NDA 208399 Varubi \(rolapitant\) inj emulsion PI FDA proposed clean 10-16-2017.pdf](#)
[NDA 208399 Varubi \(rolapitant\) inj emulsion PI FDA proposed clean 10-16-2017.docx](#)
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[NDA 208399 Varubi \(rolapitant\) inj emulsion PPI FDA proposed clean 10-16-17.pdf](#)
[NDA 208399 Varubi \(rolapitant\) inj emulsion PPI FDA proposed clean 10-16-17.docx](#)

Hello Seth,

Reference is made to your April 25, 2017 resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion.

On October 2, 2017, we received your proposed labeling submission (PI and PPI) to this application, and have proposed revisions that are included as an enclosure (PI and PPI). We request that you resubmit labeling (PI, PPI) that addresses these issues to the NDA by October 18, 2017 12:00 PM EST, or if possible by October 17, 2017.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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have received this document in error, please notify us immediately by telephone at (301) 796-0260. Thank you.

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/s/

MARY H CHUNG
10/16/2017

From: [Chung, Mary](#)
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 rolapitant inj. emulsion- PMR/PMC
Date: Wednesday, September 27, 2017 4:31:56 PM

Hello Seth,

Reference is made to your April 25, 2017 resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion.

We have the following proposed Post Marketing Requirements (PMR) and Post Marketing Commitment (PMC) for this application. Please confirm your agreement with these requirement(s) and commitment(s), including agreement with the proposed milestone dates. We request that you provide your response by October 3, 2017 or before.

Post Marketing Requirements

A confirmatory intravenous GLP toxicology study in juvenile rats
Final Report Submission: 12/2017

A GLP segmented dosing toxicology study in juvenile rats

Draft Protocol Submission: 12/2017
Final Protocol Submission: 03/2018
Study/Trial completion: 11/2018
Final Report Submission: 03/2019

A phase 3, multicenter, randomized, double-blind, placebo-controlled study of the safety, efficacy, and pharmacokinetics of Varubi (rolapitant) injectable emulsion for the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric patients ages 0-17 years old

Final Protocol Submission: 1/2019
Study/Trial Completion: 06/2024
Final Report Submission: 10/2024

An in vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 28 days after a single dose administration of Varubi (rolapitant) intravenously and document when inhibition is resolved

Draft Protocol Submission: 01/2018
Final Protocol Submission: 04/2018
Study/Trial Completion: 10/2019
Final Report Submission: 04/2020

Post Marketing Commitments

In vitro studies to evaluate the inhibitory potential of Varubi (rolapitant) on MATE1 and OATP1B1 transporters and the IC₅₀ values for each transporter

Draft Protocol Submission: 02 /2018
Final Protocol Submission: 05 /2018

Study/Trial Completion: 02 /2019
Final Report Submission: 04 /2019

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
09/28/2017

From: [Chung, Mary](#)
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 rolapitant inj. emulsion - PI and PPI
Date: Tuesday, September 26, 2017 11:11:04 AM
Attachments: [NDA 208399 rolapitant inj. emulsion PI FDA comments 9-26-17 clean.pdf](#)
[NDA 208399 rolapitant inj. emulsion PI FDA comments 9-26-17 clean.docx](#)
[NDA 208399 rolapitant inj. emulsion PI FDA comments 9-26-17 tracked changes.pdf](#)
[NDA 208399 rolapitant inj. emulsion PI FDA comments 9-26-17 tracked changes.docx](#)
[NDA 208399 rolapitant inj. emulsion PPI FDA comments 9-26-17 clean.pdf](#)
[NDA 208399 rolapitant inj. emulsion PPI FDA comments 9-26-17 clean.docx](#)
[NDA 208399 rolapitant inj. emulsion PPI FDA comments 9-26-17 tracked changes.pdf](#)
[NDA 208399 rolapitant inj. emulsion PPI FDA comments 9-26-17 tracked changes.docx](#)

Hello Seth,

Reference is made to your April 25, 2017 resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion.

On April 25, 2017, we received your proposed labeling submission (PI and PPI) to this application, and have proposed revisions that are included as an enclosure (PI and PPI). We request that you resubmit labeling (PI, PPI) that addresses these issues to the NDA by October 3, 2017 or before.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
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48 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARY H CHUNG
09/26/2017

From: [Chung, Mary](#)
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 rolapitant inj. emulsion - carton/container label
Date: Monday, September 25, 2017 4:17:08 PM

Hello Seth,

Reference is made to your April 25, 2017 resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion.

We have the following comments and recommendations for your proposed carton/container label submitted on September 18, 2017.

We request that you resubmit carton/container labeling that addresses these issues by October 3, 2017 to the NDA.

1. Immediate container and carton 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 as it was displayed on the previous container label and carton labeling.
2. Carton labels:
 - Display lot number and expiration date as “Lot:” and “Exp:”.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
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/s/

MARY H CHUNG
09/26/2017



NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: David A. Lust
Executive Director Regulatory Affairs CMC
1000 Winter Street North, Suite 3300
Waltham, MA 02451

Dear Mr. Lust:

Please refer to your New Drug Application (NDA) dated and received April 25, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Rolapitant Injectable Emulsion, 166.5 mg/92.5 mL (1.8 mg/mL).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by close of business **Monday, September 25, 2017**, in order to continue our evaluation of your NDA.

Information request:

- The Agency counter-proposed In Vitro Drug Release (IVDR) acceptance criteria (based on an overall mean of all 7 batches including the pivotal biobatch No. 22901.001 from (b) (4) as follows:
 - At 15 minutes: (b) (4) %
 - At 60 minutes: (b) (4) %
 - At 180 minutes: No less than (NLT) (b) (4) %
- If you agree, provide your agreement response by Sep 25, 2017 and revise Module 3.2.P.5.1 Drug Specification section accordingly by adding the in vitro drug release testing acceptance criteria for release and stability testing for quality control purposes.

If you have any questions, please contact me at (240) 402 8257, or oumou.barry@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Oumou Barry, MHA, MT, ASCP
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Oumou
Barry

Digitally signed by Oumou Barry
Date: 9/20/2017 08:00:50PM
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NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: David A. Lust
Executive Director Regulatory Affairs CMC
1000 Winter Street North, Suite 3300
Waltham, MA 02451

Dear Mr. Lust:

Please refer to your New Drug Application (NDA) dated and received April 25, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Rolapitant Injectable Emulsion, 166.5 mg/92.5 mL (1.8 mg/mL).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by close of business **Wednesday, September 13, 2017**, in order to continue our evaluation of your NDA.

Information request:

- Provide updated in-process controls and tests in Module 3.2.P.3.4.
- Please provide (1) information about the - brand and model number of the equipment used for (b) (4), (2) detailed sample preparation procedures for testing (b) (4).
- Explain why there (b) (4).
- Please justify why a (b) (4). Provide updated analytical method incorporating the above changes.

If you have any questions, please contact me at (240) 402 8257, or oumou.barry@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Oumou Barry, MHA, MT, ASCP

Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Oumou
Barry

Digitally signed by Oumou Barry
Date: 9/11/2017 11:30:09AM
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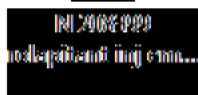
Chung, Mary

From: Chung, Mary
Sent: Tuesday, September 05, 2017 1:08 PM
To: Seth Miller (smiller@tesarobio.com)
Cc: Chung, Mary
Subject: NDA 208399 rolapitant inj. emulsion - carton/container label

Hello Seth,

Reference is made to your April 25, 2017 resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion.

We have the attached comments and recommendations for your proposed carton/container label.



We request that you resubmit carton/container labeling that addresses these issues by September 18, 2017 or before to the NDA.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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A. Carton Labeling and Container Labels

- a. Revise the presentation of the established name to read:

Varubi
(rolapitant)
injectable emulsion

- b. Revise the statement “(b) (4)” to read as “One single-dose vial” to emphasize this important administration information^a.
- c. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product barcode to each individual carton and container label as required per 21CFR 201.25(c)(2) and resubmit the proposed labeling.
- d. Drug product name should be displayed as shown below:
Varubi (rolapitant) injectable emulsion
- e. The equivalency statement to indicate the amount of active moiety related to the amount of active ingredient (b) (4) should be added to the side panel of the carton and container labeling for Varubi injection. The equivalency statement would read as follows, using the same format as shown, which is consistent with (b) (4)

Each vial contains:
Rolapitant.....166.5 mg
(equivalent to 185 mg of rolapitant hydrochloride)

If you cannot display it in the exact format due to space constraints please provide a statement to that effect.

- f. Net content of the vial should be displayed as “Net Content: 92.5 mL”
- g. Replace the statement “ Usual Dose: see Prescribing Information” with “See package insert for dosage information”

B. Carton Labeling

- a. We recommend revising the “Instructions for Administration of Varubi Injectable Emulsion” information on the back panel to increase emphasis and clarity of this important information. We recommend this to be consistent throughout all labeling:
- VARUBI injectable emulsion is homogeneous (no shaking required) and translucent white in appearance.
 - Inspect VARUBI injectable emulsion for particulate matter and discoloration prior to administration; discard if present. Do not use if contamination is suspected.
 - Use and maintain aseptic technique while handling VARUBI injectable emulsion.
 - Administer the dose by inserting a vented intravenous set through the septum of the vial. Once the stopper is punctured, use immediately. ***Do not dilute Varubi injectable emulsion.***
 - Infuse 92.5 mL from the vial over 30 minutes.
 - Varubi injectable emulsion is compatible with the following intravenous fluids through a Y-site connection:
 - o Sodium chloride 0.9% injection, USP
 - o Dextrose 5% injection, USP
 - o Dextrose 5% in Lactated Ringer’s injection, USP
 - o Lactated Ringer’s injection, USP

^a Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

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/s/

MARY H CHUNG
09/05/2017



NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: David A. Lust
Executive Director Regulatory Affairs CMC
1000 Winter Street North, Suite 3300
Waltham, MA 02451

Dear Mr. Lust:

Please refer to your New Drug Application (NDA) dated and received April 25, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Rolapitant Injectable Emulsion, 166.5 mg/92.5 mL (1.8 mg/mL).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comment and information requests. We request a written response by **Thursday, September 7, 2017**, in order to continue our evaluation of your NDA.



(b) (4)

4. Please provide method validation report for the  (b) (4) method.

5. Please provide batch numbers in a tabular format for the (b) (4) images you provided in Appendix B.

If you have any questions, please contact me at (240) 402 8257, or oumou.barry@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Oumou Barry
Regulatory Business Process Manager, Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

Digitally signed by Luz Rivera
Date: 8/24/2017 11:07:05AM
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NDA 208399

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

TESARO, Inc.
1000 Winter Street North, Suite 3300
Waltham, MA 02451

ATTENTION: Seth Miller, MPH
Director, Regulatory Affairs

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated and received April 25, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rolapitant Injectable Emulsion, 166.5 mg/92.5 mL (1.8 mg/mL).

We also refer to your correspondence, dated and received April 25, 2017, requesting review of your proposed proprietary name, Varubi.

We have completed our review of the proposed proprietary name, Varubi and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 25, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nicholas Miles, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-7025. For any other information regarding this application, contact Mary Chung, PharmD, Regulatory Project Manager in the Office of New Drugs at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
07/21/2017



NDA 208399

INFORMATION REQUEST

Tesaro, Inc.
Attention: Seth H. Miller, MPH
Director, Regulatory Affairs
1000 Winter Street North, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated and received on April 25, 2017 submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a written response by close of business **Wednesday July 12, 2017** in order to continue our evaluation of your NDA.

Drug Manufacturing Process:

A. Please clarify the following:



(b) (4)

[REDACTED] (b) (4)

Note:

1. Refer to Table 8 in the resubmission package;
2. Calculated from the data presented in the exhibit batch record [REDACTED] (b) (4) [REDACTED]);
3. Calculated from the data presented in the commercial batch record [REDACTED] (b) (4) [REDACTED]

Please address the following:

- Explain the observed discrepancy and indicate the acceptance limit for the rate of [REDACTED] (b) (4);
 - If appropriate, tighten the operating range for the rate of [REDACTED] (b) (4) in the master batch record.
- C. We understand that the amount of [REDACTED] (b) (4) [REDACTED] that support your observed in-vitro drug release profile.
- D. We recommend that you provide a detailed description of the [REDACTED] (b) (4) [REDACTED]
- E. Please indicate the batch numbers associated with [REDACTED] (b) (4) images that was provided in the resubmitted application. We recommend that you provide additional [REDACTED] (b) (4) images to support your proposed globule size.

Biopharmaceutics:

1. We acknowledge that you are proposing to use in vitro release profiles comparison to bridge the products manufactured at [REDACTED] (b) (4) [REDACTED] (b) (4) and [REDACTED] (b) (4) [REDACTED] (b) (4) requirement, you need to submit a biowaiver request to waive the requirement for submitting evidence of in vivo bioavailability or bioequivalence. It should be noted that granting of the biowaiver request will be determined upon a thorough review of your NDA resubmission based on the totality of the data submitted.

2. [REDACTED] (b) (4)
3. We recommend you to conduct the following additional studies due to concerns with respect to selectivity of the [REDACTED] (b) (4) and submit a detailed study report to the Agency:
- a. [REDACTED] (b) (4)
- b. [REDACTED]
4. We acknowledge your reported change to the initial Sample Concentration in Bulk Medium from [REDACTED] (b) (4) mg/mL to [REDACTED] (b) (4) mg/mL. However, several inconsistencies were noted to the description of initial concentration throughout the submission. For example; in Table 1 of IVDR Method Development Report, you listed [REDACTED] (b) (4) mg/mL as the sample concentration in Bulk Medium; however, you still reported [REDACTED] (b) (4) mg/mL as standard concentration in the same table. Clarify whether or not [REDACTED] (b) (4) mg/mL is the standard concentration.
5. Please clarify whether in vitro release profile data is available for the biobatch that was used in the IVDR test method. This biobatch could be the batch that was used in the pivotal in vivo pharmacokinetic (PK) study (Study No. PR-11-5016-C) comparing the proposed IV emulsions vs the oral tablets.

If available, we recommend that you submit the IVDR data of the biobatch to the agency for review. If this data is not available, provide supporting data with justification to demonstrate that the biobatch is manufactured in the same way as other (stability) batches manufactured at the previous [REDACTED] (b) (4) manufacturing facility.

6. In general, the % of drug dissolved is based on the total amount claimed (as [REDACTED] (b) (4) %). However, your calculation of a mean of [REDACTED] (b) (4) % release is based on the [REDACTED] (b) (4) drug concentration that attained equilibrium at [REDACTED] (b) (4) hour time point (Refer to Table 5, P.17/56 of your submission dated 04/25/17).

We recommend that you calculate the amount of drug release up to 5 hours and report release profile data in terms of % of total amount you added to the testing medium.

If you have any questions, please do not hesitate to contact me at (240) 402-8257 or email me at Oumou.barry@fda.hhs.gov.

Sincerely,

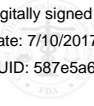
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LCDR Oumou Barry, MT (ASCP), MHA
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Oumou
Barry

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 05/18/2017 11:13:23 AM

To: smiller@tesarobio.com

CC: Oumou.barry@fda.hhs.gov; Mary.chung@fda.hhs.gov

BCC:

Subject: INFORMATION REQUEST NDA 208399, please respond by Friday June 2, 2017

NDA 208399

TESARO, Inc.

Attention: Seth H. Miller, MPH

Director, Regulatory Affairs

1000 Winter Street North, Suite# 3300

Waltham, MA 02451

Please refer to your submission dated and received on March 11, 2016 and your amendments.

The Product Quality review team has the following comments and information requests. We request a written response by 5:00 PM (EST) Friday June 2, 2017, in order to continue our evaluation of your submission.

Please provide your response via email to me Oumou.barry@fda.hhs.gov followed by an official amendment.

Drug Manufacturing Process:

- Please provide the exhibit batch record for the commercial scale batch (Batch #D006065,

(b) (4)

Facility:

We acknowledge that your response to Facility Inspections (in Section 1.11.1, Quality Information Amendment) states that (b) (4)

will not be utilized as a commercial manufacturer and you will submit an appropriate post approval supplement to list it as a manufacturer. Your response, however, does not elaborate on the roles and responsibilities of the following 2 sites which were included in the original submission:

1. [REDACTED] (b) (4) (FEI# [REDACTED])
[REDACTED] (b) (4) conducting raw material testing, drug substance acceptance testing, drug product release and stability testing.

2. [REDACTED] (b) (4) [REDACTED] (FEI# [REDACTED])
[REDACTED] (b) (4) listed as an alternative site for drug product release and stability testing, stability sample storage and testing.

Moreover, none of the 3 sites above are listed on the Form FDA 356h. Please clarify the status of each of these sites and submit an updated Form FDA 356h.

Mary Chung remains your main regulatory contact for this submission. Please copy Mary on your email response to me. Please acknowledge this communication upon receipt. Feel free to contact me by phone: (240) 402-8257 or via email: Oumou.barry@fda.hhs.gov if you have any questions.

Regards,



NDA 208399

MEETING MINUTES

TESARO, Inc.
Attention: Seth H. Miller
Director, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion.

We also refer to the telecon between representatives of your firm and the FDA on March 22, 2017. The purpose of the meeting was to discuss your proposed plans to address the deficiencies identified in the January 11, 2017 Complete Response letter.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A, teleconference
Meeting Category: End of Review

Meeting Date and Time: March 22, 2017 3:00 PM to 4:00 PM EST

Application Number: NDA 208399
Product Name: rolapitant injectable emulsion
Indication: 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 adults

Sponsor/Applicant Name: Tesaro, Inc.

Meeting Chair: Anil Rajpal, M.D.
Meeting Recorder: Mary Chung, PharmD.

FDA ATTENDEES

Division of Gastroenterology and Inborn Error Products

Donna Griebel, M.D.	Director
Anil Rajpal, M.D.	Medical Team Lead
Aisha Johnson, M.D.	Medical Reviewer
Tamal Chakraborti, Ph.D.	Pharmacology Reviewer
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff
Mary Chung, PharmD.	Senior Regulatory Project Manager

Office of Clinical Pharmacology/Division of Clinical Pharmacology III

Christine (Yuen-Yi) Hon, Ph.D.	Clinical Pharmacology Team Lead, Acting
Insook Kim, Ph.D.	Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality

Hitesh Shroff, Ph.D.	Application Team Lead
Albert (Tien Mien) Chen, Ph.D.	Biopharmaceutics Team Lead
Hansong Chen, Ph.D.	Biopharmaceutics Reviewer
Eric Adeeku, Ph.D.	Microbiology Reviewer
Nallaperumal Chidambaram, Ph.D.	Process Team Lead
Yuesheng Ye, Ph.D.	Process Reviewer

SPONSOR ATTENDEES

Mary Lynne Hedley, Ph.D.	President and Chief Operating Officer
Jeffrey Hanke, Ph.D.	Executive Vice President R&D and Chief Scientific Officer
Jennifer Jackson, Ph.D.	Senior Vice President Regulatory Affairs & Quality Assurance
Stephen Ruddy, Ph.D.	Vice President Pharmaceutical Development
David Lust, M.S.	Executive Director Regulatory Affairs CMC
Simon McGurk, Ph.D.	Executive Director Drug Product Development
Seth Miller, M.P.H.	Director Regulatory Affairs
Kelly Neelon, Ph.D.	Director Drug Product Development
John Chaber, Ph.D.	Director Analytical Development
Kenneth Douville, M.S.	Senior Manager Regulatory Affairs CMC

1.0 BACKGROUND

On March 11, 2016, Tesaro submitted NDA 208399 rolapitant injectable emulsion with the proposed indication of 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 adults. Rolapitant injectable emulsion is the I.V. formulation of the approved NDA 206500 Varubi (rolapitant) tablets.

On January 11, 2017, a complete response was issued for NDA 208399 rolapitant injectable emulsion because an adequate in vitro release method and data were not provided, and in the absence of such data, an in vivo BE study was required to support Sponsor's proposed manufacturing facility.

On February 7, 2017, Sponsor submitted an end of review meeting request to discuss their proposed plans to address the deficiencies identified in the January 11, 2017 Complete Response letter. This meeting was granted and the background package was received with the meeting request. The meeting was initially scheduled for March 14, 2017, then the meeting date was revised to March 22, 2017.

2.0 DISCUSSION

The format of these minutes provides for Tesaro's questions in regular typeface, followed by the Agency's March 8, 2017 responses in **bolded** print. The March 22, 2017 meeting discussion/comments are presented in *italic and bolded* print.

Question 1:

Does the Agency agree that the selected method development parameters are sufficient to adequately define an IVDR assay for rolapitant injectable emulsion?

FDA Response to Question 1:

Your proposed method development parameters appear reasonable. The IVDR method development report will be reviewed thoroughly upon your NDA resubmission.

Question 2:

Does the Agency agree that

(b) (4)

(b) (4)

FDA Response to Question 2:

It is premature to answer this question without data. Please note that adequacy of the data is a review issue. We recommend that you provide data to show how (b) (4) at different ranges will impact IVDR. In addition, you should propose a set of critical in-process manufacturing conditions (e.g., (b) (4)) for the intended commercial manufacturing process to ensure integrity of the finished product as well as consistent drug release throughout shelf-life of the product.

Discussion Summary:

See discussion summary for Question 4

Question 3:

Does the Agency agree that

(b) (4)

(b) (4)

FDA Response to Question 3:

No, we do not agree. We recommend that you use at least six samples (n=6)/batch to evaluate the effect of (b) (4) on the IVDR profile.

Question 4:

Does the Agency agree that

(b) (4)

(b) (4)

FDA Response to Question 4:

We are unable to give a definitive answer until we know whether your proposed method has sufficient discriminatory power to differentiate any changes in process. Therefore, this is a review issue.

Discussion Summary:

Sponsor presented their responding comments (see attached slides). FDA inquired about the nominal range (b) (4) in the formulation based on available in-house data, which does not impact the IVDR. Sponsor indicated this is to be provided as part of the planned resubmission.

FDA indicated the (b) (4) are manufacturing process parameters that are related with the manufacturing step for (b) (4). These critical process parameters can have an impact

on critical drug product properties (e.g., globule size), which in turn will impact the in vitro release profile. FDA indicated, however, the impact of these is closely related with the operating ranges. Sponsor's slide shows that (b) (4)

[Redacted]

(b) (4)
[Redacted]

Question 5:

Does the Agency agree that

(b) (4)

FDA Response to Question 5:

We cannot give you a definitive answer at this time. However, we have the following comments:

- [Redacted]
- [Redacted]
- [Redacted]

Discussion Summary:

Sponsor provided their responding comments (see attached slides). FDA requested Sponsor to provide justification for the selected (b) (4) and also to submit the validation data. FDA also indicated if Sponsor has further in vitro release data/information available in house based on other (b) (4), to provide the data to the Agency for review.

FDA recommended that Sponsor conduct globule size analysis at several time points over a period of 24 hours (e.g., 1, 3, 6, 12, 18, and 24 hours) based on one set of (b) (4) (n=6). FDA specified there should be 6 samples for each time point. Sponsor agreed.

Post-meeting Comment:

It is common to use an HPLC method to test for assay, but we are not clear how this method is used to analyze the size of globules. We recommend that other scanning

electron microscopic methods should be evaluated to determine the size and distribution of your globules.

Question 6:

Does the Agency agree that completion of the specified method validation approach will result in an appropriately validated IVDR method?

FDA Response to Question 6:

Your proposal appears reasonable. However, the IVDR method development report will be reviewed thoroughly upon your NDA resubmission.

Question 7:

Does the Agency agree that comparison of the three referenced batches manufactured at (b) (4) with the three referenced batches manufactured at (b) (4) (f_2 results to be provided in a 3 by-3 matrix) with submission of all related calculations and raw data will satisfy the Agency request?

FDA Response to Question 7:

Yes, we agree.

Question 8:

Does the explanation of (b) (4) batch numbering process resolve the question associated with batch number D003419 reported to the Agency?

FDA Response to Question 8:

Yes, we agree.

Question 9:

Does the Agency agree that the (b) (4)

FDA Response to Question 9:

No, we do not agree. We consider your proposed (b) (4)

To support your single-point release specification for the proposed IVDR method, you need to provide evidence that the product behaves in vivo as an immediate release product after IV administration.

The acceptability of the proposed in vitro release specification(s) for your product will be made during the NDA review process based on the totality of the dissolution data provided.

Discussion Summary:

FDA agreed with the Sponsor's proposed plan to set a 3-point in vitro release specification. However, Sponsor needs to provide sufficient data to support the selection of these three time points.

FDA indicated the acceptability of the proposed in vitro release specification(s) for the proposed product will be made upon a thorough review of the NDA resubmission based on the totality of the in vitro release data.

Question 10:

Does the Agency agree that the results of IVDR testing, drug product release testing and the specified physicochemical parameters for comparability are sufficient to establish a bridge between (b) (4) and (b) (4)

FDA Response to Question 10:

Yes, we agree.

Question 11:

Does the Agency agree with the proposed strategy to (b) (4)

FDA Response to Question 11:

See our previous responses. This will be a review issue.

Question 12:

Does the agency agree that (b) (4)

FDA Response to Question 12:

We acknowledge your question and would like to reconfirm that based on facility information provided in your resubmission, appropriate review and assessment will be conducted to determine the acceptability of all active sites listed to support approval of the application.

3.0 ADDITIONAL COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ATTACHMENTS AND HANDOUTS

Sponsor provided the attached handout for the March 22, 2017 meeting.

18 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARY H CHUNG
04/04/2017

From: [Chung, Mary](#)
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 rolapitant- Advice/Information Request
Date: Tuesday, November 15, 2016 2:22:57 PM

Hello Seth,

Reference is made to your New Drug Application (NDA) dated March 11, 2016 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injection.

Additional reference is made to your September 1, 2016 and July 22, 2016 responses to our August 29, 2016 and July 14, 2016 information requests (IR). Further reference is made to your amendments provided in response to our October 18, 2016 and September 22, 2016 information requests.

We have the following comments.

1. As indicated on October 18, 2016, an adequate bridge between the oral rolapitant reference tablet and the to-be-marketed I V emulsion formulation to be manufactured at the proposed (b) (4) site has not been established. We would like to reiterate that you will need to conduct another relative BA study comparing the system exposures (Cmax and AUC) using the final to-be-marketed I.V. emulsion product manufactured in your listed (b) (4) site to the oral reference tablet product. This study should have the same design elements as Study PR-11-5016-C, including the measurement of the major active metabolite.

Based on the information currently available, including the preliminary *in vitro* release data from the (b) (4) in your rolapitant injectable emulsion drug product, the comparative *in vitro* release study alone will not be considered sufficient to support the manufacturing site change from the (b) (4) site to the proposed (b) (4) site. Because the clinical safety information for higher Cmax was collected using the emulsion formulation manufactured at the (b) (4) site, you will need to bridge (i.e., a relative BA study) between the I.V. emulsion formulations manufactured at the (b) (4) site and at the proposed (b) (4) site.

You may choose to conduct a relative BA study with three treatments: oral rolapitant reference tablet, the I.V. emulsion manufactured at the (b) (4) site and the I.V. emulsion manufactured at (b) (4)

2. Reference is made to your pending responses to Clinical Pharmacology IRs dated 10/18/16 and 9/22/16, and Biopharmaceutics IRs dated 8/29/16 and 7/14/16. If you intend to provide a response to these IRs to be reviewed during the current review cycle, we request you

submit full responses (i.e., an update on status to provide or a commitment to provide in the future will not be acceptable) that are ready for review no later than November 22, 2016.

Please confirm receipt of this correspondence.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
11/15/2016



NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: Seth Miller
Director, Regulatory Affairs
1000 Winter St. #3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Varubi (rolapitant) injection emulsion.

We also refer to your August 31, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We have the following Microbiology Information Request:

1. *It is acknowledged that container closure integrity test (CCIT) was described. It is also noted that a 'critical leak test' was also described. However, describe how the positive control(s) used for the CCIT were prepared and provide data summaries for the CCIT that includes the result for the (b) (4) media fills samples tested, the positive and negative controls.*
2. *Regarding the microbiological monitoring of the manufacturing environment:*
 - a. *It is specified that (b) (4) is used to (b) (4) during manufacturing. Please describe the periodic or routine monitoring methods used for (b) (4) and provide the frequency of monitoring.*
 - b. *Explain the differences between the bulk bioburden specifications and the bulk bioburden action level. Please provide the bulk bioburden data for the exhibit batches of the drug product that were manufactured.*

3. *Regarding bacterial retention studies and (b) (4) validation:*



(b) (4)

4. *It is acknowledged that acceptable description was provided for the*

(b) (4)



If this information is located in any DMF, please provide a dated letter of authorization for access to this DMF. If any of this data is located in any SOP, provide that SOP.

5. *Regarding the 2008 initial qualification and the requalification of the*

(b) (4)



(b) (4)

(b) (4)

(b) (4)

6. *It is acknowledged that in case of a media fill failure investigations are performed to determine the root cause and determine appropriate to be taken. Describe the decision making process regarding the hold/disposition/release of products potentially affected by a media fill failure including the responsible personnel.*

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.
Please respond by November 21, 2016.

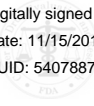
Sincerely,

Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Truong
Quach

Digitally signed by Truong Quach
Date: 11/15/2016 03:44 31PM
GUID: 5407887a000a1c163198a394481b0ee6



From: [Chung, Mary](#)
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 rolapitant inj.- Clinical Pharmacology Information Request
Date: Tuesday, October 18, 2016 3:09:39 PM

Hello Seth,

Reference is made to your New Drug Application (NDA) dated March 11, 2016 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injection.

We have the following request for additional information:

In your Response to IR#1 issued on September 22, 2016, you indicated that the measured rolapitant concentrations in plasma from the four phase 1 studies including the pivotal BE/BA study represent total drug concentrations, i.e., the sum of rolapitant [REDACTED] (b) (4) [REDACTED] and rolapitant released from them (bound and unbound to plasma protein). Please address how the plasma concentrations of rolapitant released [REDACTED] (b) (4) [REDACTED] in the pivotal BA/BE study (PR-11-5016-C) would be comparable to those from reference product (oral tablet).

We request to receive your response to the above to the NDA by October 21, 2016.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
10/18/2016

From: [Chung, Mary](#)
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 rolapitant inj. - Information Request
Date: Tuesday, October 18, 2016 11:16:30 AM

Hello Seth,

Reference is made to your New Drug Application (NDA) dated March 11, 2016 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injection.

Additional reference is made to your September 1, 2016 and July 22, 2016 responses to our August 29, 2016 and July 14, 2016 information requests, wherein you indicated your position in response to our request for an *in vitro* release method for release and stability testing for your drug product.

Because of the lack of *in vitro* data quantifying the rate and extent of release of rolapitant from the (b) (4) in your rolapitant injectable emulsion drug product, the equivalence between the I.V. formulation manufactured at the (b) (4) site (b) (4) and the to-be-marketed I.V. formulation manufactured at (b) (4) site cannot be assured. Consequently, an adequate bridge between the oral rolapitant and the to-be-marketed I.V. formulation cannot be made. Therefore, you need to conduct another relative BA study comparing the system exposures (C_{max} and AUC) using the final to-be-marketed I.V. product manufactured in your listed (b) (4) site to the oral reference product. This study should have the same design elements as Study PR-11-5016-C. However, your assay method(s) should allow measurements of the total rolapitant in the plasma as well as rolapitant (b) (4). Please indicate your plan on conducting this study.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
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/s/

MARY H CHUNG
10/18/2016



NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: Seth Miller
Director, Regulatory Affairs
1000 Winter St. #3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Varubi (rolapitant) injection emulsion.

We also refer to your March 03, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We have the following process Information Request:

Regarding the manufacturing process data provided for the new manufacturing site at (b) (4) (manufacturing information submitted on August 31, 2016):

1. (b) (4) *Please clarify this inconsistency by listing all the batches that were manufactured, their size and batch number in a tabular format. Please provide the exhibit batch record(s) in English.*
2. *The executed batch records submitted were in (b) (4) We recommend that you provide a complete English translation.*
3. *We note significant difference in the bill of materials between the exhibit batch record (page 5) and the master batch record (page 4). For example, the amount of rolapitant provided in the master batch record was (b) (4) while it was*

(b) (4) in the exhibit batch record. Please clarify whether our understanding is incorrect and revise as appropriate.

4. (b) (4) Please clarify the correct range and list in the in-process controls table in Section 3.2.P.3.5.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov. Please respond by **October 27, 2016**.

Sincerely,

Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Truong
Quach -S

Digitally signed by Truong
Quach -S
DN: cn=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=PDQPA,
email=Truong.Quach-S,
ou=2342-19002488, 1.1=2016
11 19 15
Date: 2016.10.18 15:51:51 -0400

From: Chung, Mary
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 rolapitant inj.- Clinical Pharmacology Information Request
Date: Thursday, September 22, 2016 12:57:00 PM

Hello Seth,

Reference is made to your New Drug Application (NDA) dated March 11, 2016 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injection.

Additional reference is made to your September 1, 2016 response to information request. We have the following requests for additional information:

1. Clarify whether the measured rolapitant concentrations in your phase 1 studies (PR-11-5012-C, PR-11-5022-C, PR-11-5016-C, PR-11-5021-C) for the IV formulations represent total drug concentrations (i.e., sum of rolapitant (b) (4) and rolapitant released from the (b) (4)) or only drugs that have been released from the (b) (4). The supporting data should also be provided.
2. Provide data on the stability of the globule of (b) (4) and micelles in human plasma.
3. Indicate the globule size/size distribution (mean, median, min and max, and batch number) of the IV product used in the four phase 1 studies.

We request to receive your response to the above to the NDA by September 26, 2016.

Please confirm receipt of this correspondence.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
10/18/2016



NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: Seth Miller
Director, Regulatory Affairs
1000 Winter St. #3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Varubi (rolapitant) injection emulsion.

We also refer to your March 03, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Product Information Request:

Please add the tests and acceptance limits for the following drug product attributes, justification of specification and submit the revised drug product specification table (Sec. 3.2 P 5.1).

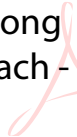
- 1. Globule size*
- 2. Heavy metals*
- 3. Leak test for container integrity*
- 4. Free fatty acids*
- 5. Content uniformity per USP <905>*

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.
Please respond by September 06, 2016.

Sincerely,

Truong Quach, Pharm. D.

Truong
Quach -
S



Digitally signed by Truong
Quach -S
DN: c=US, o=U.S.
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Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: Seth Miller
Director, Regulatory Affairs
1000 Winter St. #3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Varubi (rolapitant) injection emulsion.

We also refer to your July 29, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

BioPharm Information Request:

A simple in vitro release method of rolatiptant from its (b) (4) into the medium is sought for drug specification to be employed for release and stability testing of your drug product.

Therefore, a question was raised:

Have you tried to develop an in vitro release method using USP dissolution method with basket or paddle in various speeds and media?

If yes, submit your release method development report to the Agency for review. If not, develop your in vitro release method on the apparatus, rotational speeds, and media tested including your release data profile (individual, mean, standard deviation (SD), and CV%, and mean profile; n=12 units/batch) on the biobatch and stability batches, and submit the complete report with a proposed release acceptance criterion to the Agency for review.

It should be noted that since

(b) (4)

is not to be used.

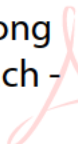
An additional IR from Process:

(b) (4)

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.
Please respond by September 09, 2016.

Sincerely,

Truong
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Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Chung, Mary

From: Chung, Mary
Sent: Thursday, August 25, 2016 9:49 AM
To: Seth Miller (smiller@tesarobio.com)
Cc: Chung, Mary
Subject: NDA 208399 rolapitant injection- Nonclinical Information Request

Hello Seth,

Reference is made to your New Drug Application (NDA) dated March 11, 2016 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injection.

We have the following requests for additional information:

1. Final report of the "Controlled Extraction Studies of (b) (4)";
2. Final report of the "Controlled Extraction Studies with (b) (4)";
3. Final report of the "Simulated Use Study of Container-Closure Components with Rolapitant Injectable Emulsion Vehicle"
4. Provide justifications for not conducting Extractable/Leachable studies with the new container closure system

We request to receive the above information to the NDA as soon as possible, and no later than August 29, 2016.

Please confirm receipt of this correspondence.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
marv.chung@fda.hhs.gov

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/s/

MARY H CHUNG
10/22/2017



NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: Seth Miller
Director, Regulatory Affairs
1000 Winter St. #3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Varubi (rolapitant) injection emulsion.

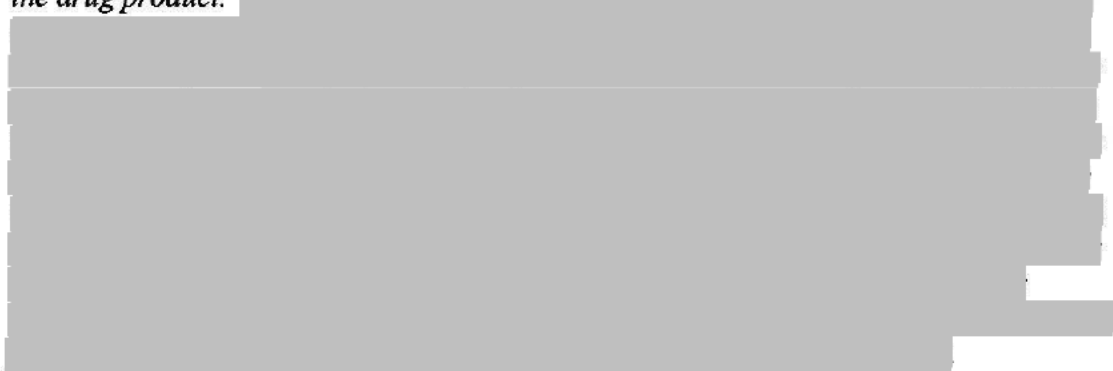
We also refer to your July 29, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Microbiology Information Request:

Your recent submission (07/29/2016) is acknowledged. Regarding validation of the container closure integrity test (CCIT) method, note that it is not a requirement to use product containing vials for the test. However, it is a requirement to use the exact same container closure system (vials, stoppers and/or seals) that is going to be used to package the drug product.

(b) (4)





If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.
Please respond by August 11, 2016.

Sincerely,

Truong
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Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: [Chung, Mary](#)
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 rolapitant injection- Clinical Pharmacology Information Request
Date: Tuesday, July 26, 2016 1:52:09 PM

Hello Seth,

Reference is made to your New Drug Application (NDA) dated March 11, 2016 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injection.

Your submission dated March 11, 2016 and Response to Information Request dated June 13, 2016 are currently under review and we have the following requests for additional information:

1. Please submit the following documents related to your response dated June 13, 2016 to Division IR #5 (i.e., ClinPharm, issue #5 from the 5/24/16 74 day correspondence): data sets, software, and codes used to conduct the PK simulation for rolapitant administered intravenously (IV) every two weeks (Q2W). Please also provide a detailed simulation report including the methodology as to how the simulation was conducted, and output tables if any.
2. Please provide the IC₅₀ or Ki values of the active metabolite SCH720881 estimated for CYP2D6 if available. Address the potential for CYP2D6 inhibition by SCH720881 following single- and multiple-dose (Q2W) IV administration.

We request to receive the above information to the application by August 1, 2016, or before.

Please confirm receipt of this correspondence.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
07/26/2016

Chung, Mary

From: Chung, Mary
Sent: Monday, July 25, 2016 1:30 PM
To: Seth Miller (smiller@tesarobio.com)
Cc: Chung, Mary
Subject: NDA 208399 rolapitant injection- Nonclinical Information Request

Hello Seth,

Reference is made to your New Drug Application (NDA) dated March 11, 2016 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injection.

We have the following request for additional information:

We refer to your May 27, 2016 response to our May 24, 2016 74-day correspondence. In this response you indicated the final study report for the leachables study of samples from primary and supportive stability batches will be submitted to the NDA by July 15, 2016. Please submit this final study report to the NDA.

We request to receive the above to the NDA by July 28, 2016, or before.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
10/22/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: Seth Miller
Director, Regulatory Affairs
1000 Winter St. #3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Varubi (rolapitant) injection emulsion.

We also refer to your July 07, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Microbiology Information Request:

- 1. It is acknowledged that a 'container closure integrity study' was provided in the 07/07/2016 submission that relies on the ability of one of two analyst to detect the presence of (b) (4) in the product vial. Note that this does not address the deficiency which was sent to you. It is also noted that although a description is provided for the*

(b) (4)



2. *It is acknowledged that acceptable validation data were provided for the*



If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.
Please respond by July 29, 2016.

Sincerely,

Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Truong Quach -5

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NDA 208399

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

TESARO, Inc.
1000 Winter Street North, Suite 3300
Waltham, MA 02451

ATTENTION: Seth Miller, MPH
Director, Regulatory Affairs

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated and received March 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rolapitant Injectable Emulsion, 166.5 mg/92.5 mL (1.8 mg/mL).

We also refer to:

- Your correspondence dated and received April 29, 2016, requesting review of your proposed proprietary name, Varubi.
- Your correspondence dated and received May 9, 2016, amending your proprietary name submission.

We have completed our review of the proposed proprietary name, Varubi and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Mary Chung, Regulatory Project Manager, in the Office of New Drugs at (301) 796-0260

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
07/22/2016



NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: Seth Miller
Director, Regulatory Affairs
1000 Winter St. #3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Varubi (rolapitant) injection emulsion.

We also refer to your June 13, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In our previous IR (IR Item #7), we requested you to develop an in vitro release method for your proposed drug product. In your response (June 13, 2016), you only provided your written justification/statement that you could use (b) (4) in lieu of an in vitro release rate as an in-vitro quality control method with cited reports of other drug products. However, without submitting any in vitro study results of your own drug product, your response is not adequate.

You need to provide in vitro study results for the validated correlations between the (b) (4) and in vitro release rate for Agency's review. Upon acceptance of the established study report, we can then grant the waiver of conducting future studies if any post-approval changes.

Provide the supporting data, i.e., a validated report of the study results to the Agency for review to demonstrate how (b) (4) correlates with in vitro release rate of your proposed drug product.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.
Please respond by July 22, 2016.

Truong
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Sincerely,

Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 208399

INFORMATION REQUEST

TESARO, Inc.
Attention: Seth Miller
Director, Regulatory Affairs
1000 Winter St. #3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Varubi (rolapitant) injection emulsion.

We also refer to your March 03, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please provide data using suitable multiple analytical methods to confirm rolapitant hydrochloride is totally (b) (4) and exists as an emulsion.
2. (b) (4). We recommend that you specify the in-process controls for all identified CPPs.
3. We recommend that you provide globule (droplet) size distribution data.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.
Please respond by July 8, 2016.

Sincerely,

Truong Quach, Pharm. D.
Regulatory Business Project Manager

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Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 208399

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

TESARO, Inc.
1000 Winter Street North, Suite 3300
Waltham, MA 02451

ATTENTION: Seth Miller, MPH
Director, Regulatory Affairs

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated and received March 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rolapitant Injection, 166.5 mg.

We acknowledge receipt of your correspondence, dated and received April 29, 2016, requesting review of your proposed proprietary name, Varubi.

The user fee goal date is July 28, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Mary Chung, Regulatory Project Manager, in the Office of New Drugs at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Aleksander Winiarski, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

ALEKSANDER P WINIARSKI
05/24/2016



NDA 208399

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

TESARO, Inc.
Attention: Seth H. Miller
Director, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated March 11, 2016, received March 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for rolapitant hydrochloride injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 11, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 9, 2016.

During our filing review of your application, we identified the following potential review issues:

PHARMACOLOGY/TOXICOLOGY

1. You indicated the following on page 13 of Section 3.2.P.2 of the submission. *“For rolapitant injectable emulsion, a leachables study will be performed on selected samples from primary and supportive stability batches and validation batches stored at*

25°C/60%RH in the inverted position. Upon request, results of the leachables study will be provided during the NDA review cycle. Otherwise, they will be included in the annual update.” The final report of the leachables study must be submitted to the NDA for our review. Provide a timeline for submission of this information immediately. Submit your response to the application as soon as possible, and no later than June 13, 2016.

2. Submit toxicological evaluation of the safety of the leachables for our review and evaluation. Provide a timeline for submission of this information immediately. Submit your response to the application as soon as possible, and no later than June 13, 2016.
3. You have not provided adequate justification for the safety of (b) (4). You need to provide a comprehensive safety assessment of (b) (4) based on available toxicology information to justify the safety of (b) (4) in the drug product. Submit your response to the application by June 13, 2016.
4. The proposed specification for heavy metals in the drug substance is Not More Than (NMT) (b) (4) ppm. Based on the proposed daily dose of 185 mg of rolapitant hydrochloride, the exposure to heavy metals including (b) (4) from the drug product would be approximately (b) (4) µg/day, which exceeds the parenteral Permitted Daily Exposure (PDE) for (b) (4) µg/day) and (b) (4) µg/day) per the ICH Q3D guidance. Thus, the proposed specification for heavy metals at NMT (b) (4) ppm is not acceptable. Reduce the specification limit for heavy metals so that the daily exposure of (b) (4) µg/day, respectively. Submit your response to the application by June 13, 2016.

CLINICAL PHARMACOLOGY

5. We note that there was about two-fold increase in systemic exposure to dextromethorphan on day 28 after administration of a single dose of rolapitant compared to that after administration of dextromethorphan without rolapitant. As rolapitant could be administered as frequent as once every 2 weeks, provide additional information, including but not limited to, modeling and simulation of drug interaction potential to address the extent of inhibition of CYP2D6 after multiple doses of rolapitant. Submit your response to the application by June 13, 2016.

PRODUCT QUALITY

6. Submit your master batch record and executed batch records to the application as soon as possible, and no later than May 31, 2016.

BIOPHARMACEUTICS

7. 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 drug quality tests.

The use of the in vitro release methodology is mainly for assessing the in vitro release kinetics of rolapitant over time from the proposed drug product (performance) and for assessing the future changes in, e.g., composition/formulation, manufacturing site, the process, etc. of your drug product (quality).

Therefore, provide the following:

- A. Develop and submit an appropriate and validated in vitro release method using the simulated physiologic medium and acceptance criteria for the in vitro release of the drug from the emulsion, including:
 - a. solubility data for the drug substance as a function of pH range;
 - b. a detailed description of the release method being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, release media, agitation/rotation speed, pH, assay, sink conditions, etc.). If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. If possible, the release profile should be complete and cover at least ^(b)₍₄₎ % of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples (n=12) per testing variable;
 - c. the complete release profile data (individual raw data, mean, SD, and mean profiles) for your product. The release data should be reported as the cumulative drug release with time;
 - d. detailed batch information on your drug product employed in the study (i.e., Batch/Lot No., Manufacturing Date, Manufacturing Site, Expiration Date, Testing Date, Batch Size, etc.), and
 - e. the testing conducted to demonstrate the discriminating capability of the selected release test, as well as the supportive validation data for the release method (i.e., method robustness, etc.) and the analytical method (precision, accuracy, linearity, stability, etc.), which should be validated per USP <1092>.
- B. Release Acceptance Criteria: Provide the complete release profile data (e.g., 10, 20, and 30 minutes; 1, 2, 4, 6, 8, 10, and 12) from the clinical and stability registration batches supporting the selection of the release acceptance criteria (i.e., specification-sampling time points and specification values). For the setting of the drug release acceptance criteria, the following points should be considered:

- a. The in vitro release specifications should encompass the timeframe over which at least ^(b)₍₄₎ % of the drug is released or where the plateau of drug dissolved is reached if incomplete release is occurring. Data from the lots used in the clinical trials and primary stability studies must be used. The manufacturing information of those batches (number, date, site, and size of the batch made) should also be provided or linked to the appropriate page and volume numbers in the NDA.
- b. The release acceptance criteria should be set in a way to ensure consistent performance from lot to lot, and these criteria should not allow the release of any lots with release profiles outside those that were tested clinically.

Submit your response to potential review issue #7 to the application by June 13, 2016.

MICROBIOLOGY

Submit your response to the following microbiology issues to the application by June 13, 2016.

8. DMF ^(b)₍₄₎ is deficient. The DMF holder has been notified.
9. We acknowledge that a container closure integrity test result is provided for the registration batches using the ^(b)₍₄₎ method and the container closure system used to package the drug product. However, provide a container closure integrity test validation for the container closure system used to package the drug product that also includes a positive and a negative control and a reproducible method of detection. Describe how the test is performed and provide the sensitivity of the test.
10. Regarding the microbiological monitoring of the manufacturing environment:



(b) (4)

(b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions provided as an enclosure.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by June 24, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Mary Chung, Senior Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
05/24/2016

From: [Chung, Mary](#)
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 rolapitant inj.- Information Request
Date: Monday, May 02, 2016 12:35:57 PM

Hello Seth,

Reference is made to your New Drug Application (NDA) dated March 11, 2016 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injection.

We have the following request for additional information:

1. We acknowledge that you provided a summary of the assay validation in Study Report KB-0051-RB-BS and the laboratory method in Appendix 3. However, it is unclear if the bioanalytical assay validation report, BAC-KB-L003 referred in Study Report KB-0051-RB-BS-RPT-01 was submitted. Please provide the assay validation report BAC-KB-L003. If the report was submitted, please guide the reviewer to its location.
2. Submit analysis datasets for the pivotal bioequivalence study (PR-11-5016-C) and all other pharmacokinetics studies for the intravenous formulation (5012-C, 5022-C, and 5021-C). Provide complete source code, input files and key analysis output if applicable.
 - a. In order to facilitate our review, please provide separate PK analysis datasets by substrate for Study 5021-C.
3. To facilitate our review of the annotated label, provide the hyperlinks to the supporting data for the proposed labeling language, e.g., original study report.

We request to receive your response to the NDA by May 4, 2016.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
05/03/2016

From: [Chung, Mary](#)
To: [Seth Miller \(smiller@tesarobio.com\)](mailto:smiller@tesarobio.com)
Cc: [Chung, Mary](#)
Subject: NDA 208399 rolapitant inj.
Date: Monday, April 25, 2016 9:28:34 AM

Hello Seth,

Reference is made to your New Drug Application (NDA) dated March 11, 2016 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injection.

We have the following request for additional information:

Please provide an updated review and summary of relevant cases reported in your pharmacovigilance database, reports of pregnancies received (with details and outcomes provided) since December 26, 2014.

We request to receive your response to the NDA by May 4, 2016.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
04/25/2016



IND117307

MEETING PRELIMINARY COMMENTS

TESARO, Inc.
Attention: Jennifer Jackson, Ph.D.
Senior V.P., Global Regulatory Affairs and Quality Assurance
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Dr. Jackson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rolapitant injection.

We also refer to your October 23, 2015 correspondence, requesting a meeting to discuss the clinical and nonclinical content for your planned NDA.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, PharmD.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B, Teleconference
Meeting Category: Pre-NDA

Meeting Date and Time: January 26, 2016 9:00 AM – 10:00 AM EST

Application Number: IND 117307
Product Name: rolapitant injection
Indication: Prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

Sponsor/Applicant Name: TESARO, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 26, 2016 9:00 AM to 10:00 AM EST between Sponsor and the Division of Gastroenterology and Inborn Errors Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On October 23, 2015, TESARO requested a meeting to discuss the clinical and nonclinical content for their planned NDA for rolapitant injection. On September 1, 2015, NDA 206500 Varubi (rolapitant) tablets for oral use was approved.

The proposed indication for rolapitant for intravenous injection is identical to that of rolapitant tablets, which is prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

This meeting request was initially granted for December 16, 2015, then the meeting date was revised to January 26, 2016 per sponsor request. The background package was received December 22, 2015.

2.0 DISCUSSION

Question 1:

Does the Agency agree that the IV toxicology program presented in Section 6.1 adequately bridges to the oral program and is sufficient to support an NDA for the approval of the IV formulation?

FDA Response to Question 1:

The IV toxicology program appears to be adequate to support the NDA for the rolapitant IV formulation.

Question 2:

The sponsor considers the scope of the clinical program conducted with rolapitant IV sufficient for submission of a New Drug Application for the approval of rolapitant injectable emulsion (Section 6.2). Does the Agency agree?

FDA Response to Question 2:

Your clinical pharmacology program seems sufficient to support the submission of an NDA. The adequacy of study results will be reviewed once the NDA is submitted.

Question 3:

Does the Agency agree with the proposed presentation strategy for the Drug Abuse Liability Evaluation of rolapitant outlined in Section 6.3?

FDA Response to Question 3:

You have proposed the below plan:

Submit the final Drug Abuse Liability Evaluation from the approved NDA 206500 for oral rolapitant with an addendum containing relevant IV data. This addendum will present the analysis of abuse-related adverse events (AEs) following IV administration in the same format as reported for the oral formulation based on the following categories:

- a. Monotherapy Single Dose with IV formulation
 - I. Data will be presented by actual dose level and pooled dose level (<185 mg, 185 mg, or >185) from studies PR-11-5012-C (SAD only), PR-11-5016-C and PR-11-5022-C. Subjects who received any dose of rolapitant IV will be included into the “all Rolapitant IV dose combined” group. In addition, data from subjects receiving the 200 mg oral rolapitant reference dose in the bioequivalence study will be presented separately.

- b. Monotherapy Multiple Dose with IV formulation
- c. Drug-Drug interaction with IV formulation

Your plan is acceptable in general, however more detailed comments are provided below.

- 1. For point “a”: to clarify all adverse events from ALL single dose monotherapy patients/studies should be pooled together and presented as the table shown in Table 3, page 6 of Meeting Request, which also will include rolapitant tablets.**
- 2. For point “b”: We agree.**
- 3. For point “c”: The tables with adverse events should be presented for each drug, i.e., digoxin, sulfasalazine and Cooperstown Cocktail (Midazolam, Omeprazole, Warfarin, Caffeine, and Dextromethorphan), separately.**

Question 4:

Does the FDA agree with the contents of the 4-month safety update outlined in Section 6.4?

FDA Response to Question 4:

Your proposal to include a quarterly PADER for Varubi along with a final nonclinical study report as the contents of your 4-Month Safety Update appears reasonable given that there are no on-going clinical trials or patient exposure of rolapitant IV nor are any expected to be initiated during the NDA review.

ADDITIONAL COMMENTS

CLINICAL PHARMACOLOGY

We request that you submit datasets for plasma concentrations, pharmacokinetic parameters and PK analysis in .xpt format.

3.0 FDA ADDITIONAL COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of

Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for

industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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/s/

MARY H CHUNG
01/21/2016