CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206500Orig1s000

<u>OTHER REVIEW(S)</u>

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 206500
Product Name: Rolapitant

PMR/PMC Description: GLP toxicology study in juvenile rats

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	1/30/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   To support the marketing of rolapitant in adult patients, rolapitant was evaluated in oral nonclinical toxicity studies of up to 6 months duration in rats and up to 9 months duration in monkeys. The safety of rolapitant in juvenile animals has not been evaluated.

   The GLP toxicology study in juvenile rats is intended to support administration of the drug in pediatric patients from 0 to 17 years old.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   To support administration of rolapitant in pediatric patients from 0 to 17 years old, a juvenile animal study is needed.

   The results from this nonclinical PMR will be used for safety assessment of rolapitant dosing in pediatric patients.

Reference ID: 3813551

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☒ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

GLP toxicology study in juvenile rats

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Reference ID: 3813551

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☒ Nonclinical study, not safety-related (specify)
GLP toxicology study in juvenile rats
☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3813551

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # Product Name:	NDA 206500 Rolapitant
PMR/PMC Description:	A dose-ranging study assessing the pharmacokinetics, safety, tolerability, and effectiveness of Varubi (rolapitant) in pediatric patients ages 0-17 years old

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	2/28/2017
	Study/Trial Completion:	7/31/2020
	Final Report Submission:	11/30/2020
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   The NDA for rolapitant for adult patients is under review. The safety and efficacy have been shown in adults to support the study in pediatric patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   This is a PREA PMR study.

   [redacted] (b) (4)

Reference ID: 3813551

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☒ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   A dose-ranging study assessing the pharmacokinetics, safety, tolerability, and effectiveness of rolapitant in pediatric patients (b) (4)

   Required

   - ☐ Observational pharmacoepidemiologic study
   - ☐ Registry studies
   - ☐ Primary safety study or clinical trial
   - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   - ☐ Thorough Q-T clinical trial
   - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Reference ID: 3813551

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3813551

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 206,500
Product Name: rolapitant

PMR/PMC Description: A study to evaluate the efficacy and safety of a single oral dose of Varubi (rolapitant) in pediatric patients ages 0-17 years old

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	11/30/2020
	Study/Trial Completion:	04/30/2026
	Final Report Submission:	08/30/2026
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   The adult studies are complete and ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   This is a PREA PMR study. [redacted] (b) (4) to evaluate the efficacy and safety of a single oral dose of Varubi (rolapitant) in pediatric patients ages 0-17 years old.

Reference ID: 3813551

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☒ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   (b) (4)

   Required

   - ☐ Observational pharmacoepidemiologic study
   - ☐ Registry studies
   - ☒ Primary safety study or clinical trial
   - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   - ☐ Thorough Q-T clinical trial
   - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
   - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
   - ☐ Pharmacokinetic studies or clinical trials
   - ☐ Drug interaction or bioavailability studies or clinical trials
   - ☐ Dosing trials

Reference ID: 3813551

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3813551

PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	NDA 206500
Product Name:	Rolapitant
PMC Description:	In vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of Varubi (rolapitant)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	12/31/2015
	Study/Trial Completion:	04/30/2016
	Final Report Submission:	06/30/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

Rolapitant is a moderate CYP2D6 inhibitor with inhibitory effects observed on 7 days after a single dose administration. Co-administration of a single dose of rolapitant increased the exposure to dextromethorphan, a substrate of CYP2D6 by 2.2-fold on Day 1 and by 3.3-fold on Day 7. The inhibitory effect of rolapitant on CYP2D6 was not studied beyond 7 days after rolapitant administration.

(b) (4). However, a lack of information beyond 7 days after single dose administration (b) (4) for the duration of CYP2D6 inhibition.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3813551

Rolapitant is a moderate CYP2D6 inhibitor with inhibitory effects observed on 7 days after a single dose administration. The inhibitory effect of rolapitant on CYP2D6 was not studied beyond 7 days after rolapitant administration.

(b) (4)

This PMC will be used to inform the duration of the inhibitory effect of rolapitant on CYP2D6 enzyme to (b) (4) and to mitigate the potential risk with increased systemic exposure of concomitant CYP2D6 substrates.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☐ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 3813551

In vivo drug interaction study with a sensitive CYP2D6 substrate to evaluate the duration of an inhibitory effect on CYP2D6 activity by rolapitant beyond 7 days after a single dose administration of rolapitant. (b) (4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☒ Other
  In vivo drug interaction study with dextromethorphan, a sensitive CYP2D6 substrate.

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

Reference ID: 3813551

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3813551

PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 206500
Product Name: Rolapitant

PMC Description: In vitro studies to evaluate the inhibitory potential of Varubi (rolapitant) on renal transporters, i.e., organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE) transporters, organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3)

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	12/31/2015
	Study/Trial Completion:	04/30/2016
	Final Report Submission:	06/30/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   Inhibition of renal transporters may lead to an increase in systemic exposure of concomitant drugs that are substrates of these transporters, which include but are not limited to, metformin and cisplatin (OCT2 and MATEs), and methotrexate (OAT1, OAT3). (b) (4)

   To better understand the drug interaction potential in patients and to improve the labeling recommendation, in vitro inhibition studies need to be conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3813551

Inhibition of renal transporters may lead to an increase in systemic exposure of concomitant drugs that are substrates of these transporters, which include but are not limited to, metformin and cisplatin (OCT2 and MATEs), and methotrexate (OAT1, OAT3). (b) (4)

To better understand the drug interaction potential in patients and to improve the labeling recommendation, in vitro inhibition studies need to be conducted.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☐ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Studies to evaluate the drug interaction potential via inhibition of kidney transporters (OCT2, MATE1, (b) (4) OAT1, and OAT3) by rolapitant (b) (4)

Reference ID: 3813551

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
In vitro drug interaction studies to evaluate the inhibition of transporters expressed in kidney (OCT2, MATE1, (b) (4) OAT1, and OAT3) by rolapitant

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

Reference ID: 3813551

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3813551

PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	NDA 206500
Product Name:	Rolapitant
PMC Description:	In vitro study to evaluate the inhibitory potential of Varubi (rolapitant) on OATP1B1 and OATP1B3. The in vitro study results will determine the need for a subsequent clinical assessment of a drug interaction between Varubi (rolapitant) and other concomitant medications

PMR/PMC Schedule Milestones:	Final Protocol Submission:	2/28/2016
	Study/Trial Completion:	06/30/2016
	Final Report Submission:	08/31/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   Inhibition of hepatic transporters, OATP1B1 and OATP1B3 can cause an increase in systemic exposure of OATP substrates such as statin. The inhibitory potential of rolapitant on OATP1B1 and OATP1B3 was not evaluated to assess drug interaction potential.

   To better understand the drug interaction potential in patients and to improve the labeling recommendation, in vitro inhibition studies need to be conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Inhibition of hepatic transporters, OATP1B1, and OATP1B3 can cause an increase in systemic exposure of OATP substrates such as statin. The results from this PMC will lead to a better drug interaction assessment to inform the labeling recommendation.

Reference ID: 3813551

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☐ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Studies to evaluate the drug interaction potential via inhibition of OATP1B1, and OATP1B3 by rolapitant. If deemed necessary based on the in vitro study results, a clinical drug interaction study may follow. (b) (4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials

Reference ID: 3813551

☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
In vitro drug interaction studies to evaluate the inhibition of OATP1B1, and OATP1B3 by rolapitant

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Reference ID: 3813551

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/s/

MARY H CHUNG
08/31/2015

DONNA J GRIEBEL
08/31/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 7, 2015
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 206500
Product Name and Strength:	Varubi (Rolapitant) Tablets, 90 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Tesaro, Inc.
Submission Date:	September 5, 2014
OSE RCM #:	2014-2148
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Kendra Worthy, Pharm.D.

1 PURPOSE OF MEMO

The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the revised container label (Appendix A) to determine if it is

Reference ID: 3788863

acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container label is acceptable from a medication error perspective.

[1]Abraham, A. Label and Labeling Review for Varubi (NDA 206500). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 04 29. 32 p. OSE RCM No.: 2014-2148.

Reference ID: 3788863

APPENDIX A. LABEL AND LABELING SUBMITTED ON JUNE 19, 2015

(b) (4)

Reference ID: 3788863

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/s/

SHERLY ABRAHAM
07/07/2015

KENDRA C WORTHY
07/07/2015

STUDY ENDPOINT CONSULT REVIEW

STUDY ENDPOINTS TRACKING NUMBER	AT-2014-191
IND/NDA/BLA NUMBER	NDA 206500
LETTER DATE/SUBMISSION NUMBER	September 5, 2014
PDUFA GOAL DATE	September 1, 2015
DATE OF CONSULT REQUEST	November 13, 2014
REVIEW DIVISION	DGIEP
MEDICAL REVIEWER	Aisha Peterson/ Ruyi He
REVIEW DIVISION PM	Mary Chung
STUDY ENDPOINTS REVIEWER(S)	Michelle Campbell
ASSOCIATE DIRECTOR, STUDY ENDPOINTS (ACTING)	Elektra Papadopoulos
REVIEW COMPLETION DATE	4/8/2015
ESTABLISHED NAME	Rolapitant
TRADE NAME	
SPONSOR/APPLICANT	Tesaro, Inc.
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
ENDPOINT(S) CONCEPT(S)	No significant nausea and QoL
MEASURE(S)	Nausea Visual Analog Scale and FLIE
INDICATION	Prevention of (b) (4) delayed nausea and vomiting in emetogenic cancer chemotherapy
INTENDED POPULATION(S)	Adults on emetogenic cancer chemotherapy

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/s/

MICHELLE L CAMPBELL
05/05/2015

ELEKTRA J PAPADOPOULOS
05/12/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 8, 2015
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	BRAND NAME (rolapitant)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 206500
Applicant:	Tesaro, Inc.

1 INTRODUCTION

On September 5, 2014, Tesaro, Inc. submitted for the Agency's review New Drug Application (NDA) 206500 for BRAND NAME (rolapitant) tablets, with the proposed indication for use in adults in combination with other antiemetic agents for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on September 19, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BRAND NAME (rolapitant) tablets.

2 MATERIAL REVIEWED

- Draft BRAND NAME (rolapitant) tablets PPI received on October 7, 2014 and received by DMPP and OPDP on April 24, 2015.
- Draft BRAND NAME (rolapitant) tablets Prescribing Information (PI) received on September 5, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 24, 2015.
- Approved AKYNZEO (netupitant and palonosetron) capsules comparator labeling dated October 10, 2014.
- Approved Emend (aprepitant) capsules Prescribing Information comparator labeling dated August 12, 2014.
- Approved Emend (aprepitant) capsules Patient Package Insert comparator labeling dated March 20, 2013.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
05/08/2015

ADEWALE A ADELEYE
05/08/2015

SHAWNA L HUTCHINS
05/08/2015

LASHAWN M GRIFFITHS
05/08/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 8, 2015

To: Mary Chung, Pharm.D., Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., Team Leader, OPDP

Subject: NDA # 206500 - rolapitant tablets, for oral use

Reference is made to DGIEP's consult request dated September 19, 2014, requesting review of the proposed Package Insert (PI), Patient Package Insert (PPI), and Carton/Container Labeling for rolapitant tablets, for oral use.

OPDP has reviewed the proposed PI entitled, "NDA 206500 rolapitant SCPI 4-24-15 Tracked Changes.doc" that was sent via email from DGIEP to OPDP on April 24, 2015. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling entitled, "carton-varubi-180.pdf" that was available in the EDR at \\CDSESUB1\evsprod\NDA206500\0014, on May 7, 2015. OPDP has no comments at this time on the proposed Carton/Container labeling.

Please note that comments on the proposed PPI were provided on May 8, 2015 under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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/s/

ADEWALE A ADELEYE
05/08/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Erica Radden, M.D.
Division of Pediatric and Maternal Health,
Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Pediatric Team Leader,
Division of Pediatric and Maternal Health,
Office of New Drugs

Lynne Yao, M.D., Acting Director,
Division of Pediatric and Maternal Health,
Office of New Drugs

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Rolapitant

Application Number: NDA 206500

Sponsor: Tesaro, Inc.

Proposed Indication: Indicated in adults for use in combination with other antiemetic agents for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy

Proposed Dosage form and Route of administration: (b) (4) mg immediate release tablets administered orally

Proposed Dosing regimen: (b) (4) mg given orally on Day 1, 1-2 hours prior to initiation of chemotherapy in conjunction with a corticosteroid and a 5-HT3 receptor antagonist

Reference ID: 3746798

Consult Request: DGIEP requests Division of Pediatric and Maternal Health (DPMH) participation in the labeling discussions, and assistance in preparation for the Pediatric Review Committee.

Materials Reviewed:

- Division of Pediatric Maternal Health (DPMH) consult request
- Sponsor's proposed labeling for (December 9, 2014)
- Prior DPMH review for rolapitant (IND 72754) dated July 6, 2014
- Agreed upon initial Pediatric Study Plan for rolapitant, IND 72754 (September 4, 2014)

Background:
Rolapitant, a new molecular entity, is a neurokinin 1 (NK1) antagonist with the proposed indication for use in adults in combination with other antiemetic agents for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of em cancer chemotherapy (CINV).

Regulatory Background:
The sponsor submitted an NDA for rolapitant on September 5, 2014. The submission of this NDA triggers the Pediatric Research and Equity Act (PREA) as a new active ingredient. The Agency filed an agreed upon iPSP on September 4, 2014 for deferral of studies in patients birth to 17 years of age. (See the prior DPMH consult review for rolapitant, IND 72754 dated July 6, 2014 for further discussion on the pediatric development plan.) Table 1 and Table 2 below provide a summary of all planned nonclinical and clinical pediatric studies.[1]

Table 1: Proposed Nonclinical Studies for rolapitant

PLANNED NONCLINICAL STUDIES		
Species	Type of Study	Comments
Rat	Exploratory dose range finding study	Dose selection for the confirmatory GLP study
Rat	Confirmatory GLP toxicology study in juvenile animals	To support initiation of clinical studies in children ages 0 – 18 yr

GLP= Good Laboratory Practice

[1] Agreed upon initial Pediatric Study Plan for rolapitant, IND 72754 (September 4, 2014)

Reference ID: 3746798

Table 2: Proposed Clinical Studies for rolapitant

PLANNED PEDIATRIC CLINICAL STUDIES		
Pediatric PK/PD and Clinical Effectiveness Studies		
Age Group	Type of Study	Comments
0-<18 years	Phase 1 PK/PD dose ranging and clinical effectiveness	To determine appropriate dose(s) based on analysis of exposure-response relationships in adults and pediatrics and modeling/simulation approaches
Age Group	Type of Study	Comments
(b) (4)		

PK = pharmacokinetics; PD = pharmacodynamics; R = randomized; DB = double-blind; AC = active-controlled

DGIEP requests DPMH-Pediatrics team assistance in providing labeling recommendations for pediatric use, and preparing for the Pediatric Review Committee (PeRC) meeting.

DPMH Review of labeling:
The DPMH-Pediatrics team labeling review will focus on edits to subsection 8.4 (Pediatric Use). The DPMH- Maternal Health team will provide labeling recommendations for pregnancy and lactation (subsections 8.1 and 8.2) in a separate review.

Pediatric Use Labeling:
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. (Also see draft Guidance for Industry and

Reference ID: 3746798

Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013.)

Sponsor's proposed labeling dated December 9, 2014:

> **8.4 Pediatric Use**
> Safety and efficacy of BRAND NAME have not been established in pediatric patients.

Discussion on Pediatric Labeling Recommendations:
Rolapitant has not been studied and is not approved for use in the pediatric population. Furthermore, no safety concerns have been noted that would preclude studies or use in pediatric patients. Therefore, the proposed language for the Pediatric Use subsection is appropriate.

Conclusion:
The sponsor's proposed labeling for the Pediatric Use subsection is appropriate based on 21 CFR 201.57(c)(9)(iv).

DPMH reviewed the sponsor's draft labeling and participated in the internal meetings between October, 2014 and May, 2015. DPMH also assisted in preparation for PeRC. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

Reference ID: 3746798

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/s/

ERICA D RADDEN
05/04/2015

HARI C SACHS
05/04/2015

LYNNE P YAO
05/05/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: May 4, 2015 **Date consulted:** September 16, 2014

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Acting Division Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Varubi (rolapitant hydrochloride) Tablets

NDA: 206500

Applicant: Tesaro, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For use in adults in combination with other antiemetic agents for the prevention of (b) (4) delayed nausea associated with initial and repeat courses of emetogenic cancer chemotherapy.

Materials Reviewed:

- DPMH consult request dated September 16, 2014, DARRTS Reference ID 3628717
- Sponsor's submitted background package for NDA206500, Rolapitant

Reference ID: 3746601

Consult Question:
DGIEP requests DPMH assistance in completing the review of the pregnancy and lactation section of labeling.

INTRODUCTION

Varubi (rolapitant hydrochloride (HCl)) is a Neurokinin 1 (NK_1) receptor antagonist. On September 5, 2014, Tesaro, Inc., submitted a 505 (b)(2) new drug application (NDA) 206500 for rolapitant HCl tablets for the proposed indication of prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. Rolapitant HCl is indicated for use in adults in combination with other anti-emetics.

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on September 16, 2014, to provide input for appropriate labeling of the pregnancy and lactation subsections of rolapitant HCl labeling.

BACKGROUND

Rolapitant HCl and Drug Characteristics

Rolapitant HCl is an NK_1 receptor antagonist. Substance P is the preferred endogenous ligand at NK_1 receptors. Substance P is a regulatory peptide found in the gastrointestinal tract and regions of the central nervous system implicated in the vomiting reflex. NK_1 receptor antagonists have demonstrated activity against both peripheral and central emetic stimuli in animal models.[1]

Rolapitant HCl has the following characteristics:

- Molecular weight: 554.95 Daltons
- Half-life: 169-18(b) (4) hours
- Volume of distribution: 460 L/kg
- Bioavailability: 100%
- Protein Binding: 99.8%

Pregnancy and Nursing Mothers Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[2] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006

[1] Gan, et al. Rolapitant for the Prevention of Postoperative Nausea and Vomiting: A Prospective, Double-Blinded, Placebo-Controlled Randomized Trial. Anesthesia & Analgesia. 2011; 112 (4): 804-812.
[2] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

Reference ID: 3746601

Physicians Labeling Rule[3] format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Nonclinical Experience

In animal reproduction studies, there were no teratogenic effects or embryo-fetal toxicity observed with oral administration of rolapitant HCl during the period of organogenesis at doses up to 1.2 times and 2.9 times the MRHD in rats and rabbits, respectively. See Nonclinical review for details.[4]

Rolapitant HCl and Pregnancy

A search of published literature for available human pregnancy data was performed to update the Pregnancy subsection of labeling for this NDA. No studies or data with rolapitant use in pregnant women were found. Although the sponsor did not conduct studies with rolapitant HCl in pregnant women, there were three pregnancies that occurred during Phase 1 and Phase 2 of the rolapitant study:

- Study P04852[5]:
  In a two-part Phase 1 QT/QTc study for rolapitant, there were 184 patients included in the study. Part 1 was a randomized, placebo-controlled, third-party blind (subjects were blinded with respect to treatment, but not to the dose level), parallel group, single-dose, dose escalation study to assess the safety and tolerability of a single high dose of rolapitant. Part 2 was a randomized, placebo and positive controlled, double blind, double dummy, parallel group study. Parts 1 and 2 were conducted in healthy adult volunteers. There was one pregnancy reported.
  - 26 year-old female (subject 000306) received one dose of rolapitant 800 mg orally on October 17, 2007. She was found to have a positive pregnancy test on November 7, 2007. There is no information on the pregnancy outcome of this patient.

- Study P04937 (5.3.5.4)[6]
  In the Phase 2 randomized, double-blind, double-dummy, dose-ranging, active and placebo-controlled study, 619 subjects were included in the study and there were two pregnancies reported.
  - A 32 year-old female (subject 016-1284) underwent abdominal myomectomy and chromopertubation due to uterine fibroids and was given one dose of rolapitant 200 mg orally and ondansetron placebo IV before surgery, on (b) (6), to prevent postoperative nausea and vomiting. The patient had a negative serum and urine pregnancy test prior to surgery but two to three weeks after surgery had a positive pregnancy test. An ultrasound done on June 5, 2008, showed a gestation of 7 weeks and 2 days. The patient went on to deliver a premature baby boy (about 35 weeks) via elective cesarean section. There were no details regarding why the infant was born prematurely. The pregnancy was complicated by gestational diabetes, and the

[3] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).
[4] Rolapitant NDA 206500, Tracy Behrsing, Ph.D., Nonclinical Review, March 19, 2015.
[5] Rolapitant Oral NDA 206500, Tesaro Response to Request for Information received 2/3/2015.
[6] Rolapitant Oral NDA 206500, Tesaro Response to Request for Information received 2/3/2015.

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infant had hypoglycemia soon after birth due to maternal gestational diabetes. The infant was otherwise healthy and had no fetal malformations.

- A 25 year-old female (subject 032-1314) underwent exploratory laparotomy and wide excision of an abdominal wall endometrioma due to endometriosis. The patient received one dose of rolapitant 70 mg orally and ondansetron placebo intravenously prior to surgery on (b) (6) for prevention of postoperative nausea and vomiting. When the patient returned for follow-up on (b) (6), her menstrual cycle was late, and a pregnancy test was positive. The patient went on to deliver a healthy baby girl weighing 3860 grams and measuring 20.5 inches in length. Apgar scores were 7 and 9 at one and five minutes, respectively. The gestational age at delivery was not provided. There were no pregnancy complications and no fetal malformations noted.

Reviewer Comments
There have been no studies with rolapitant HCl done in pregnant women, and the two women who became pregnant during the phase two studies had unremarkable pregnancies. In addition, animal reproduction studies have not demonstrated teratogenic effects or embryo-fetal toxicity.

The patient (subject 000306) in the phase I study was given a very high dose of rolapitant (800mg), which is not a typical dose of rolapitant (180mg given one to two hours prior to chemotherapy) that will be given to patients. In an information request response, the applicant noted that there is no pregnancy outcome information for subject 000306. The applicant contacted the principal investigator for study P04852 who is currently attempting to gather documentation stored at a long term storage facility. The sponsor will update the FDA once this information has been located.

Rolapitant HCl and Lactation
A search of published literature for available human lactation data was performed to update the Lactation subsection of labeling for this application. No studies or data with rolapitant HCl use in lactating women were found.

Post-natal studies in rats have shown that rolapitant HCl is present in rat milk. Radioactivity from labeled [^{14}C] rolapitant hydrochloride was transferred into milk of lactating rats. The mean milk/plasma radioactivity concentration ratios in dams at 1 to 48 hours post-dose ranged from 1.24 to 3.25. Based on average daily consumption of milk (b) (4) (2 mL/day) and the maximum milk radioactivity determined, pup exposure is expected to be 0.32% of the orally administered dose.[7]

Reviewer Comments:
The characteristics of rolapitant HCl suggest that the drug may be present in breast milk. Rolapitant HCl has a low molecular weight (MW) of 554.95 Daltons, which may lead to movement of rolapitant into breast milk. The high volume of distribution (V_d) of 460 L/kg

[7] Rolapitant HCl sponsor proposed labeling, Section 8.2: Lactation.

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and a long half-life (about 7 days), increases the presence of the drug in the mother's circulation and may increase the risk of infant exposure to rolapitant via breast milk.[8]

Rolapitant HCl is present in rat milk. (b) (4) *rolapitant HCl has characteristics that suggest that it has the potential to be present in human breast milk* (b) (4) *There are, however, no significant adverse events noted in adults who took rolapitant HCl during clinical trials. Therefore, DPMH recommends the following statement be included in labeling:*

> *"The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRAND NAME and any potential adverse effects on the breastfed infant from BRAND NAME or from the underlying maternal condition or the use of concomitant chemotherapy."*

Rolapitant HCl and Infertility

A search of published literature for available fertility data was performed to update the Females and Males of Reproductive Potential subsection of rolapitant HCl labeling, and no human data were found.

In a fertility and early embryonic development study in female rats, rolapitant hydrochloride at an oral dose 0.2 times the MRHD, there were slight decreases in the number of corpora lutea and implantation sites. Rolapitant hydrochloride did not affect the fertility or general reproductive performance of male rats at doses 4.9 times the MRHD.[9] The applicant (b) (4)

Reviewer Comments:
The finding (slight decrease in the number of corpora lutea) noted in female rats was reversible and, it is unlikely that this finding is clinically relevant. In addition, this drug is only indicated with the use of chemotherapeutic agents, which are more likely to impact fertility. (b) (4)

CONCLUSIONS AND RECOMMENDATIONS

Rolapitant HCl labeling has been updated to comply with the PLLR. A review of published literature revealed no data with rolapitant HCl use in pregnant or lactating women. DPMH has the following recommendations for rolapitant HCl labeling:

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[8] Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.
[9] Rolapitant HCl applicant proposed labeling, Section 13: Nonclinical Toxicology.

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- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of rolapitant HCl labeling was formatted in the PLLR format to include "Risk Summary" and "Data" subsections.[10]
- **Lactation, Section 8.2**
  - The "Lactation" subsection of rolapitant HCl labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" subsection.[11]

Because the applicant has voluntarily complied with the PLLR requirements prior to the June 30, 2015 effective date, language waiving the current labeling requirements should be included in the approval letter. The following approval letter language is suggested.

(b) (4)

We are waiving the current requirements of 21CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), regarding the content and format of labeling for subsections (b) (4) Your approved labeling for subsections 8.1, 8.2, (b) (4) reflects the content and format requirements of the Pregnancy and Lactation Labeling Rule (79 FR 72063, December 4, 2014) which implements on June 30, 2015."

DPMH ROLAPITANT HCL LABELING

DPMH discussed our labeling recommendations with DGIEP at a labeling meeting on March 24, 2015. DPMH and the DGIEP Nonclinical team recommendations are below. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here. (See Appendix A for the applicant's proposed pregnancy and nursing mothers labeling.)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on BRAND NAME use in pregnant women to inform any drug associated risks. In animal reproduction studies, there were no teratogenic or embryo-fetal effects observed with oral administration of rolapitant hydrochloride in rats and rabbits during the period of organogenesis at doses up to 1.2 times and 2.9 times, respectively, the maximum recommended human dose (MRHD) *[see Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

[10] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

[11] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

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Data

Animal data

The potential embryo-fetal toxicity of rolapitant hydrochloride was assessed in pregnant rats administered oral doses equivalent to up to 22.5 mg/kg/day rolapitant free base throughout organogenesis. Rats administered doses equivalent to 13.5 or 22.5 mg/kg/day rolapitant free base exhibited evidence of maternal toxicity including decreased body weight gain and/or body weight loss and a concomitant decrease in food consumption during the first week of dosing. No teratogenic or embryo-fetal effects were observed at doses equivalent to up to 22.5 mg/kg/day rolapitant free base (approximately 1.2 times the recommended human dose on a body surface area basis). In rabbits administered rolapitant hydrochloride throughout the period of organogenesis, oral doses equivalent to up to 27 mg/kg/day rolapitant free base (approximately 2.9 times the recommended human dose on a body surface area basis) were without effects on the developing fetus.

The pre- and postnatal developmental effects of rolapitant hydrochloride were assessed in rats administered oral doses equivalent to 2.25, 9 or 22.5 mg/kg/day rolapitant free base during the periods of organogenesis and lactation. Maternal toxicity was evident based on mortality/moribund condition, decreased body weight and food consumption, total litter loss, prolonged parturition, decreased length of gestation, and increased number of unaccounted for implantation sites at a dose equivalent to 22.5 mg/kg/day free base (approximately 1.2 times the recommended human dose on a body surface area basis). Effects on offspring at this dose included decreased postnatal survival, and decreased body weights and body weight gain, and may be related to the maternal toxicity observed. At a maternal dose equivalent to 9 mg/kg/day rolapitant free base (approximately 0.5 times the recommended human dose on a body surface area basis), there was a decrease in memory in female pups in a maze test and a decrease in pup body weight.

8.2 Lactation

Risk Summary

There are no data on the presence of rolapitant in human milk, the effects of rolapitant in the breastfed infant, or the effects of rolapitant on milk production. (b) (4) rolapitant hydrochloride administered orally to lactating female rats was present in milk *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRAND NAME and any potential adverse effects on the breastfed infant from BRAND NAME or from the underlying maternal condition or the use of concomitant chemotherapy.

Data

(b) (4)

Radioactivity from labeled [^{14}C] rolapitant hydrochloride was transferred to the milk of lactating rats following a single oral dose equivalent to 22.5 mg/kg rolapitant free base, and the maximum radioactivity in milk was observed at 12 hours post-dose. The mean milk/plasma radioactivity concentration ratios in dams at 1 to 48 hours post-dose ranged from 1.24 to 3.25. Based on average daily consumption of milk (2 mL/day) and the maximum milk radioactivity determined, pup exposure is expected to be 0.32% of the orally administered dose.

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APPENDIX A – Applicant's Proposed Varubi Pregnancy and Lactation Labeling
FULL PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

Data

Animal Data

The potential embryo-fetal toxicity of rolapitant hydrochloride was assessed in pregnant rats administered oral doses (b) (4) Rats administered (b) (4) exhibited evidence of maternal toxicity including decreased body weight gain and/or body weight loss and a concomitant decrease in food consumption during the first week of dosing. No teratogenic or embryo-fetal effects were observed at up to (b) (4) In rabbits administered rolapitant hydrochloride throughout the period of organogenesis, oral doses up to (b) (4) were without effects on the developing fetus.

The pre- and post-natal developmental effects of rrolapitant hydrochloride were assessed in rats administered oral doses (b) (4) during the periods of organogenesis and lactation. Maternal toxicity was evident based on (b) (4) (b) (4)

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(b) (4)

8.2 Lactation

Risk Summary

(b) (4)

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRAND NAME and any potential adverse effects on the breastfed (b) (4) from BRAND NAME or from the underlying maternal condition or the use of concomitant chemotherapy.

Data

(b) (4)

Radioactivity from labeled [^{14}C] rolapitant hydrochloride was transferred into milk of lactating rats following a single oral dose (b) (4) Maximum radioactivity in milk was observed at 12 hr post-dose.

Based on average daily consumption of milk (2 mL/day) and the maximum milk radioactivity determined, pup exposure is expected to be 0.32% of the orally administered dose. (b) (4)

(b) (4)

(b) (4)

13. Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

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(b) (4)

Rolapitant hydrochloride was not genotoxic in an Ames test, a human peripheral blood lymphocyte chromosome aberration test, and a mouse micronucleus test.

(b) (4)

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/s/

MIRIAM C DINATALE
05/04/2015

LYNNE P YAO
05/05/2015

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 5, 2015

To: Donna Griebel, M.D., Director
Division of Gastroenterology and Inborn Errors Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Pharmacologist
Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: Rolapitant (SCH 619734; Varubi)
NDA 206,500 (IND (b) (4))
Indication: prevention of chemotherapy-induced nausea and vomiting (CINV)
Sponsor: Tesaro, Inc.
PDUFA Goal Date: July 5, 2015

Materials reviewed: Abuse-related preclinical and clinical data in NDA (submission #000, 9/5/14)

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1. Background

This memorandum responds to a consult request to CSS by the Division of Gastroenterology and Inborn Errors Products (DGIEP) to evaluate abuse-related preclinical and clinical data submitted in NDA 206,500 for rolapitant (Varubi). The Sponsor is Tesaro, Inc.

Rolapitant (SCH 619734 hydrochloride monohydrate) is a new molecular entity that acts as a competitive inhibitor of the neurokinin-1 (NK-1) receptor site (the site of action of the neurotransmitter substance P). There are three drug products containing NK-1 antagonists that have been approved by FDA: aprepitant (Emend), fosaprepitant (an intravenous form of aprepitant, Emend Injection) and rolapitant (in combination with the 5HT3 antagonist, palonosetron, as Akynzeo). None of these drugs were determined to have abuse potential during a CSS review of the abuse-related data in their respective NDAs. Thus, none of these drugs are scheduled under the Controlled Substances Act. (b) (4)

The Sponsor is seeking approval to market (b) (4) two 90 mg oral tablets of rolapitant for a single oral dose of 180 mg one or two hours prior to the initiation of chemotherapy. Since chemotherapy typically consists of multiple exposures to anti-neoplastic agents over multiple cycles, rolapitant will be used by patients on a chronic basis. It is notable that throughout drug development, the dose of rolapitant as expressed as being two 100 mg tablets. However, on February 12, 2015, DGIEP informed the Sponsor that the strength of rolapitant should be expressed in terms of the active moiety (rolapitant) due to the new USP salt policy. This necessitated that the dose be expressed as two 90 mg tablets.

To date, approximately 2800 individuals have received rolapitant in 20 completed clinical trials, which includes 808 healthy volunteers (primarily acute dose studies) and 1567 cancer patients, with a total of 5335 exposures to rolapitant. The studies include 14 Phase 1 studies, 13 conducted in healthy adults and one conducted in adults with mild or moderate hepatic impairment; two Phase 2 studies of rolapitant in subjects at risk for chronic idiopathic cough (CIC) and postoperative nausea and vomiting (PONV), and four clinical studies of rolapitant in subjects at risk for CINV, including three conducted in subjects receiving highly-emetic chemotherapy (HEC) and one conducted in subjects receiving moderately-emetic chemotherapy (MEC).

The investigations with cancer patients were effectively conducted as acute dose studies since patients received single doses of rolapitant during each chemotherapy treatment cycle, typically separated by 3-4 weeks. Thus, the clinical studies do not represent multiple dose exposures in terms of closing spacing of doses (e.g., daily administration).

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2. Conclusions

a) In primate self-administration and physical dependence studies, there were no signals of abuse or withdrawal.

b) Clinical safety data related to abuse potential is very limited, so conclusions about abuse potential cannot be drawn.

c) Physical dependence and withdrawal symptoms in humans were not evaluated.

3. Recommendations

CSS recommends that:

(b) (4)

b) Rolapitant should not be recommended for scheduling under the Controlled Substances Act.

c) (b) (4)

4. Discussion

A. Chemistry of Rolapitant

Rolapitant (5S,8S)-8-[[(1R)-1-[3,5-bis(trifluoromethyl)phenyl] ethoxy]methyl]-8-phenyl-1 ,7-diazaspiro[4.5]decan- 2-one hydrochloride hydrate monohydrate). Rolapitant hydrochloride monohydrate is a white to off-white (b) (4) It is insoluble in water and sparingly soluble in aqueous solution at the physiologic pH of 7.4. It has low solubility in 0.1N hydrochloric acid and in simulated gastric fluid (pH 2-4), but good solubility in ethanol and propylene glycol. The molecular formula is $C_{25}H_{27}ClF_6N_2O_2$ with a molecular weight of 554.95. Its CAS number is 552292-08-7.

B. Pharmacology of Rolapitant

1. Receptor Binding Studies (Study #21202, 21203, 21204)

Rolapitant and its major metabolite (SCH 720881) binds with high affinity to the human NK1 receptor (Ki = 0.66 nM). Neither parent nor metabolite have significant affinity (>

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50% inhibition) for other CNS abuse-related sites, including: GABA (benzodiazepine, GABA), sigma, cannabinoid (CB-1, CB-2), dopamine (D1, D2, D3, D4, D5), serotonin (5HT1A, 2A, 2B, 2C, 3, 5A, 6 and 7), channels (calcium, potassium, chloride), and transporters (dopamine, norepinephrine, serotonin, GABA).

2. Preclinical Behavioral Studies

a. Functional Observational Battery with Rolapitant (Study #03124)

Study Design

Male rats (n = 6) received a single oral gavage dose of 5, 25 or 100 mg/kg and female rats (n = 6) received a single oral gavage dose of 1, 5 or 25 mg/kg. Differential dosing between the sexes was based on a pharmacokinetic study showing a 4-fold greater exposure in females than in males. Saline served as the negative control. The animals were observed using a standard functional observational battery for 4 hours after drug administration.

Results

Rolapitant did not induce any behavioral changes in either male or female rats in home cage observations, handling observations, open field observations, sensory observations, neuromuscular observation, physiological observations, locomotor observations or body weights.

Conclusions

There were no abuse-related behavioral observations following administration of rolapitant.

b. Self-Administration Study (Study #2013-001)

The self-administration study in rats is a pivotal animal behavioral study for abuse potential assessment and is reviewed in detail. The Sponsor conducted a self-administration drug study in which rolapitant was tested for its ability to induce self-administration as a measure of the rewarding property of the drug.

Study Design

Rhesus monkeys (n = 6) were trained to self-administer cocaine (0.18 mg/kg/infusion, i.v.) under a fixed ratio 30 (FR30) schedule of reinforcement in 2-hour trials. Following stable self-administration of cocaine, the dose of cocaine was varied (0.056, 0.1, 0.18, 0.32 and 0.56 mg/kg/infusion, i.v.) over the 5-day sessions with cocaine. Saline sessions (using FR30 and 2-hour trials) followed for 5 days after cocaine sessions to demonstrate extinction using a substance without rewarding properties. At the conclusion of the

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saline sessions, cocaine was reintroduced for 5 days to demonstrate reinstatement, followed by a second 5-day phase of extinction sessions with saline.

At the end of the training period, rolapitant sessions commenced, using 4 doses (0.1, 0.5, 1.0 and 1.5 mg/kg/infusion, i.v.) in 2-hour trials with an FR30 schedule of reinforcement. Each dose will be available for 3 days during daily trials. Each 3-day period will be followed by 3-day cocaine and saline sessions. Rolapitant dosing was initiated with the lowest proposed dose of 0.1 mg/kg/injection. Based on toxicological and pharmacokinetic studies in monkeys, the maximum allowable daily cumulative dose based on self-administration was set at 7.5 mg/kg.

The doses of rolapitant were selected based on calculations of how many infusions of a particular dose would be necessary to achieve 3 times the Cmax of the human therapeutic dose (e.g., 200 mg human dose produces 1000 ng/ml, so 3X = 3000 ng/ml). These calculations were conducted on the basis of 5, 10, 15, 20 and 25 infusions, for both Day 1 and cumulatively for Day 3. In each of these calculations, at least one of the proposed doses of rolapitant produced the 3000 ng/ml Cmax. Notably, though, these calculations were estimations based on what is currently known about the pharmacokinetics.

Results

Cocaine produced a dose-dependent increase in self-administration while rolapitant was not self-administered at any dose. The lack of self-administration from rolapitant was similar to that seen following exposure to saline or vehicle.

Conclusion

Rolapitant does not appear to produce rewarding properties that would maintain self-administration.

It is notable that rolapitant has a very long half-life which poses the risk of drug accumulation. This may have skewed the interpretation of the results, if there was high self-administration at the beginning of access to rolapitant, but a decrease over time. However, animals did not self-administer rolapitant at any dose during any part of the drug access period, so this concern is not relevant.

c. Drug Discrimination Study

A drug discrimination study was not conducted with rolapitant because there are no NK-1 antagonists that have been shown to have abuse potential and are thus scheduled under the Controlled Substances Act that could serve as a training drug.

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3. Physical Dependence Study in Monkeys (Study #2013-002)

Study Design

Male Rhesus monkeys (n = 4/group) were given rolapitant (7.5 or 25 mg/kg/day) or vehicle through daily oral gavage for 28 days. The treatments were abruptly discontinued on Day 29. A 12-day drug discontinuation period was then conducted until Day 42 of the study. Notably, the study design did not include a positive control condition to validate the study.

Observations for morbidity, mortality, injury, and the consumption of food and water were conducted twice daily for all animals. Clinical observations were initiated one week prior to drug administration and continued through Day 42 (Day 12 of the drug discontinuation phase). Additionally, functional observational battery (FOB) evaluations were conducted that included assessment of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, bizarre behavior, and palpation of tissue masses, and body weights. The FOB was conducted beginning on the day prior to drug administration to establish a baseline and on Days 1, 14, and 28 for approximately 60 minutes after drug administration. During the drug discontinuation phase, FOBs were conducted twice daily on Days 29, 30, 31, 32, 33, 34 and 35. Because no signs of withdrawal were noted on Day 35, no FOBs were conducted on Day 43 and the study was terminated.

Results

(b) (4)

Conclusions

This study is not valid because (b) (4)

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However, neither dose of rolapitant (7.5 or 25 mg/kg) produced changes in behavioral signs either during drug administration or for a week after drug discontinuation, compared to vehicle. Thus, there is limited information that rolapitant does not produce physical dependence following chronic administration when compared to vehicle.

C. Pharmacokinetics

1. Animal Pharmacokinetics

In mice, rats, and monkeys maximum plasma concentrations (Cmax) were typically reached between 2-6 hours. Rolapitant exposure (area under the curve; AUC) was generally dose proportional. Elimination of rolapitant appeared faster in mice and rats than in monkeys. Gender-related differences in exposure were found in rats, with an exposure consistently higher in the female than the male (4 fold in average) following repeated dosing of rolapitant (5 mg/kg). Accumulation was minimal in mice, rats, and monkeys. Rolapitant is highly plasma protein-bound (99.7-99.9% across mouse, gerbil, rat, dog, monkey, and human). In rat studies, rolapitant was found to be extensively distributed. Rolapitant has a single major metabolite in rodents and monkeys (SCH 720881), formed through oxidation of rolapitant.

2. Human Pharmacokinetics (Study # P04328, #P03670)

Administration

The absolute bioavailability of rolapitant following oral administration was approximately 100%. For the metabolite, maximum concentrations were achieved by 120 hr post dose and were approximately 13% of rolapitant Cmax.

In a multiple-dose study of rolapitant (10, 25 and 50 mg; Study P03670), plasma concentrations of rolapitant accumulated 5-fold with repeated daily dosing and steady-state was not achieved after 10 days because of the long T1/2 of rolapitant (172-238 hours). Tmax of 2-3 hours on Day 1 and Day 10. Systemic exposure to rolapitant (Cmax and AUC0-24) increased in proportion to the increase in dose from 10 to 50 mg following single and repeat dose administration. The main active metabolite SCH720881 has Tmax 120-168 up to 336 hr and T1/2 ~up to 196. Under therapeutic conditions, rolapitant will be administered as a single dose of 200 mg in up to 6 chemotherapy treatment cycles (generally separated by 3-4 weeks).

Metabolism

Oxidation is the major route of metabolism of rolapitant, and SCH 720881 (M19) is the only metabolite detected in plasma. M5 and M9b were the major metabolites found in urine and each accounted for 1.6% of the dose. Rolapitant was the major component in

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feces (13% of the dose) with M9b, M10c, and M13 comprising 4.3, 4.8, and 3.5% of the dose, respectively. Few glucuronide conjugates were detected.

Elimination

Systemic plasma clearance (CL/F) of rolapitant following oral administration was low, 1.74 L/hr, and the volume of distribution (Vz/F) was 460 L, suggesting extensive distribution of rolapitant into peripheral tissues. Clearance following IV administration was 1.94 L/hr, and confirmed the CL/F calculated from the PO data. The T½ for rolapitant after the IV dose was long, 148 hrs, and similar to the value found after single PO dose (138 hrs).

Single Dose PK Studies

After a single dose, the oral bioavailability of rolapitant in humans was 100% (Study P04328) and systemic exposure (Cmax and AUC) increased in proportion to the dose increase from 25 to 200 mg (Study P03670). The apparent terminal elimination T1/2 was long and independent of dose, ranging, on average, from 169 to 183 hours across the doses tested. Within the therapeutic (200 mg) and supratherapeutic (>200 mg) single oral dose range, AUC of rolapitant and SCH 720881 increased in a dose proportional manner, (Study P04852). Time to Cmax was generally consistent across dose levels (rolapitant: 4-6 hours). See Table 21 in the NDA.

Multiple Dose PK Studies

Study P03670 Multiple dose. The study showed the long T½ of rolapitant of 172-238 hrs, and plasma concentrations of rolapitant increased 5-fold with repeated daily dosing and steady-state was not achieved after 10 days. Tmax was 2-3 hrs and Cmax at 50 mg dosing for 10 days was 895 ng/ml.

Systemic exposure to rolapitant (Cmax and AUC0-24) increased in proportion to the increase in dosage from 10 to 50 mg following single and repeat dose administration. See table 25 in the NDA submission.

D. Clinical Studies

To date, approximately 2800 subjects and patients received rolapitant in the 20 completed clinical trials, which includes 550 healthy volunteers and 1567 of the intended population of cancer patients. A total of 5335 exposures to rolapitant which were essentially single dose studies.

There were: 17 Phase 1 studies, 2 Phase 2 studies, and 4 Phase 3 studies.

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1. Positron Emission Tomography (PET) Study with Rolapitant (Study #P04078)

Study Design

A positron emission tomography (PET) study was conducted in 14 healthy male adults to determine whether orally administered rolapitant could displace the CNS-penetrant NK-1 radioligand ^{11}C-GR205171 as an indicator that rolapitant also crossed the blood brain barrier.

Rolapitant dosing started at 25 mg and was escalated or de-escalated with 2 subjects per dose level until the drug had consistent ≥90% occupancy. Twelve subjects received single oral doses of rolapitant at doses ranging from 5 mg to 200 mg and 2 of whom received single doses of aprepitant 125 mg. PET scans were conducted at 120 hours (5 days) postdose for those subjects receiving rolapitant and at 24 hours postdose for those subjects receiving aprepitant.

Results

Based on model predictions and calculations, plasma rolapitant concentrations above 348 ng/ml correspond to >90% NK-1 receptor occupancy, as shown by displacement of the CNS-penetrant NK-1 radioligand ^{11}C-GR205171. Occupancy of the NK-1 receptor tended to plateau above 50 mg dose. Thus, doubling the dose of rolapitant from 50 mg to 100 mg resulted in an average of only 3% increase in receptor occupancy. As expected, aprepitant also displaced ^{11}C-GR205171.

Conclusions

Rolapitant passes the blood brain barrier and acts on the NK-1 receptor in the brain. This is similar to another NK-1 antagonist, aprepitant.

2. Clinical Safety ISS

Safety and Tolerability in Healthy Volunteers

Rolapitant was evaluated in nine Phase 1 trials including bioavailability, pharmacokinetics, drug interactions, effects on ECG, and PET brain receptor study. Sponsor states that during these studies with rolapitant at doses up to 800-mg were safe and well tolerated.

Single Dose Studies

The pooled treatment-emergent adverse event data from Phase 1 single-dose oral studies in healthy adult volunteers indicates that the overall incidence of treatment-emergent AEs did not appear to be dose related; in the rolapitant 5, 10, 25 50, 400 and 800 mg dose groups, and ranged from 50% to 55% and were comparable to that in the placebo group

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(52%). The most common (≥5% of subjects) AEs were headache (15 subjects; 7%), dizziness (13 subjects, 6%), and somnolence (10 subjects, 5%).

Multiple Dose Studies

In the rising multiple-dose study, 17 (71%) of 24 subjects who received active treatment and 6 (100%) of 6 subjects who received placebo reported treatment-emergent AEs. The most frequent AEs in the combined active treatment groups were headache (5/24, 21%) and diarrhea (4/24, 17%).

Safety and Tolerability in Patients with CINV

In the Phase 2 dose-finding study in CINV, the incidence of treatment-emergent AEs during Cycle 1 was similar across all treatment groups and varied between 67% and 76%. The most common (≥10% of subjects) treatment-emergent AEs in the active treatment groups were nausea, fatigue, vomiting, constipation, and diarrhea.

Completed Phase I Clinical Studies-relevant to abuse potential

none

Phase III studies

A Total of 4 CINV studies were performed and are included in this analysis (Pooling Group 1)

- P04351 (CINV Dose-finding): All patients
- P04832 (CINV HEC): All patients
- P04833 (CINV HEC): All patients
- P04834 (CINV MEC): All patients

3. CLINICAL ABUSE POTENTIAL EVALUATION (summary):

Human abuse potential study - not performed

Human dependence evaluation:

Human dependence study - not performed
Human dependence data – not existent

Evaluation of abuse potential related adverse events in all clinical studies

For the purpose of evaluating abuse potential in NDA the analysis of AEs related to abuse potential is provided separately for:

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- healthy volunteers (single-dose; multiple-dose; drug-drug interactions)
- patients (by indication)
- Special populations (hepatically impaired subjects)

The abuse related AEs are presented for:

- Pooling Group 1 which comprises CINV patients (see table below)
- Pooling Group 2 which comprises healthy subjects receiving a single dose of rolapitant as monotherapy (see table below)
- Separate data sets for the non-CINV patient studies, selected Phase 1 studies in special population and Phase 1 studies with co-administered of other drugs, and multiple-dose trial.

Pooling Group	Subjects	Studies
Group 1	CINV patients	P04351, P04832, P04833, P04834
Group 2	Healthy subjects receiving single-dose rolapitant as monotherapy	P03670, P04328, P04852, P04854, PR-10-5000-C, PR-10-5004-C, PR-10-5007-C, PR-10-5013-C, PR-10-5014-C

Abbreviation: CINV, chemotherapy-induced nausea and vomiting

Pooling Group 1

Abuse potential related AEs from patients in this population cannot be meaningfully analyzed as they are confounded by underlying disease and/or one of multiple drugs including opiates.

Pooling Group 2

The summary of AEs in Pooling 2- Healthy subjects (N=550), (from Abuse potential section, page 79 of NDA)

Summary Table: Incidence [N%] of Potential Abuse-related AEs in Single Dose Monotherapy Trials in Healthy Volunteers (Pooling Group 2)

Type of Effect Preferred Term	Placebo (N=56)	<200mg (N=69)	200mg (N=422)	>200mg (N=59)	Rolapitant[1] (N=550)
Euphoria-Related AEs					
Feeling Drunk	0	0	1 (0.2)	0	1 (0.2)
CNS Depressant Effects					
Somnolence	1 (1.8)	4 (5.8)	23 (5.5)	2 (3.4)	29 (5.3)
Stimulation And Anxiety Symptoms					
Anxiety	0	0	0	3 (5.1)	3 (0.5)
Perceptual Disturbances/ Psychotomimetic Effects					
Abnormal Dreams	0	0	2 (0.5)	0	2 (0.4)
Disorientation	0	0	0	2 (3.4)	2 (0.4)
Hallucination, Visual	0	0	0	1 (1.7)	1 (0.2)
Nightmare	0	0	0	1 (1.7)	1 (0.2)
Paraesthesia	0	0	2 (0.5)	0	2 (0.4)

Reference ID: 3748247

<u>*Individual studies*</u>

Multiple-dose Trials (Not Included in Pooled Analysis) - Study P03670 in healthy subjects

The study consisted of 4 parts and was conducted in healthy volunteers. Only subjects in Parts 1 and 2 were included in Pooling Group 2 as they received only single doses of rolapitant.

However, in Part 3, the safety and tolerability of rising multiple doses of rolapitant administered QD for 10 days were evaluated and included a drug-drug interaction component (Part 4) in which midazolam 2 mg was administered in combination with rolapitant and alone. In Part 3 Rolapitant in doses of 10, 25, 50 mg; was given QD for 10 days to 24 healthy subjects.

One patient had somnolence and hangover.

PONV Patients (Not Included in Pooled Analysis) - Study # P04937

Study P04937 was performed in patients undergoing surgical procedures with halogenated ether-based anesthesia to prevent post-operative nausea and vomiting (PONV). This study assessed the effect of a range of rolapitant single doses (5, 20, 70, 200 mg) in the prevention of PONV post-anesthesia. The population included: placebo, 103; rolapitant 5 mg, 103; rolapitant 20 mg, 102; rolapitant 70 mg, 103; rolapitant 200 mg, 104; ondansetron, 104. Completed study included 532 subjects. Patients receiving rolapitant had following CNS adverse events: dizziness, somnolence, anxiety, insomnia, restlessness. Euphoria was not reported.

Reference ID: 3748247

Table below (from p. 329 of NDA)

	PLA N=103	R5 N=103	R20 N=102	R70 N=103	R200 N=104
DIZZINESS	6 (6)	8 (8)	11 (11)	10 (10)	14 (13)
LETHARGY	0	0	0	2 (2)	0
SOMNOLENCE	0	7 (7)	3 (3)	0	3 (3)
PSYCHIATRIC DISORDERS	15 (15)	17 (17)	9 (9)	11 (11)	16 (15)
ABNORMAL DREAMS	0	0	0	0	1 (1)
AGITATION	1 (1)	0	0	1 (1)	0
ANXIETY	5 (5)	5 (5)	3 (3)	3 (3)	6 (6)
CONFUSIONAL STATE	0	0	0	0	0
DEPRESSION	1 (1)	1 (1)	0	0	2 (2)
DISORIENTATION	0	1 (1)	0	1 (1)	0
HALLUCINATION	0	0	0	0	1 (1)
INSOMNIA	9 (9)	11 (11)	5 (5)	5 (5)	8 (8)
NIGHTMARE	0	0	1 (1)	0	0
RESTLESSNESS	0	0	0	2 (2)	0

Study # P04888 Multiple dose CIC in (Chronic idiopathic cough) Patients (Not Included in Pooled Analysis)

The study assessed the safety and effectiveness of single dose of rolapitant in reducing cough reflex following capsaicin challenge and reducing severity of cough. It was a crossover study enrolled 35 patients with CIC who received rolapitant 50 mg; design included one week of treatment with 7 days' follow-up; 1 week of crossover treatment with 7 days' follow-up, and a 6-week washout period separated treatments. CNS related AEs included: 2 patients with insomnia, 1 patient with somnolence, 1 with lethargy, 1 with anxiety. Of note, Euphoric mood was only reported in healthy volunteers in not pooled analysis group in the study # Study PR-10-5001-C in the presence of efavirenz alone and in combination with rolapitant.

4. Evaluation of dependence in clinical studies

The sponsor states that formal evaluation of withdrawal effects following discontinuation of rolapitant was not an objective of rolapitant trials; however, a review of potential abuse-related AEs in the 2 multiple-dose studies was conducted to determine if any events were reported following discontinuation of treatment. There were no AEs indicative of withdrawal in the multiple-dose CIC patient trial (P04888). One subject in the multiple-dose component of study P03670 reported a hangover 16 days after the last

Reference ID: 3748247

dose of rolapitant 25 mg, which was co-administered with a single dose of midazolam (Subject 011-1105).

5. Evaluation of diversion in clinical studies

The sponsor states that compliance records for clinical studies demonstrated very high compliance with drug administration, showing an average compliance of 102% (88-127%) in the multiple-dose outpatient study (P04888), also there was typically 100% compliance in single and multiple dose studies when administration was under supervision of clinical staff.

The sponsor is not aware of any reports of medication theft, and the available compliance data do not suggest that there has been diversion of the study medication in clinical trials.

The incidence of diversion was not evaluated in clinical trials, but, there were no reports of AEs of protocol deviations or discontinuations related to drug diversion, intentional or unintentional overdose, misuse (including non-oral routes), abuse or dependence with rolapitant capsules or tablets in clinical trials.

6. Overdose in clinical studies

There are no data on overdose with rolapitant. Single supratherapeutic doses of up to 800 mg, the maximum dose administered, were well tolerated in a study conducted in healthy volunteers. Of the 59 subjects dosed with >200 mg rolapitant, adverse events that occurred in >5% of subjects included dizziness (17%), nausea (7%), headache (7%) and anxiety (5%).

Reference ID: 3748247

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHERINE R BONSON
05/05/2015

ALICJA LERNER
05/05/2015

MICHAEL KLEIN
05/05/2015

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: May 1, 2014

TO: Mary Chung, Regulatory Project Manager
Aisha Peterson, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206500

APPLICANT: Tesaro, Inc.
DRUG: rolapitant HCl
NME: Yes
THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy

CONSULTATION REQUEST DATE: November 12, 2014
INSPECTION SUMMARY GOAL DATE: May 5, 2015
DIVISION ACTION GOAL DATE: September 4, 2015
PDUFA DATE: September 4, 2015

I. BACKGROUND:

Tesaro, Inc. submitted this NDA for rolapitant, a substance P/neurokinin-1 (NK-1) receptor antagonist for the indication of use in combination with other antiemetic agents for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.

The review division requested inspection of three Phase 3 protocols and one Phase 2 protocol that were submitted in support of the NDA:

1. Protocol TS-P04832 entitled, "A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study of the Safety and Efficacy of Rolapitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Subjects Receiving Highly Emetogenic Chemotherapy (HEC)",

2. Protocol TS-P04833 entitled, "A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study of the Safety and Efficacy of Rolapitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Subjects Receiving Highly Emetogenic Chemotherapy (HEC)",

3. Protocol TS-P04834 entitled, "A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study of the Safety and Efficacy of Rolapitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Subjects Receiving Moderately Emetogenic Chemotherapy (MEC)", and

4. Protocol P04351 entitled "A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Dose Finding Study to Determine the Safety and Efficacy of SCH 619734 for the Treatment of Chemotherapy- Induced Nausea and Vomiting (CINV) in Subjects Receiving Highly Emetogenic Chemotherapy (HEC)".

Sites were chosen for inspection based on high enrollment, efficacy outcome, and previous inspectional history.

II. RESULTS (by Site):

Type of Inspected Entity, Name and Address	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification*
CI: Agnieszka Jagiello-Gruszfeld, M.D. Al. Wojska Polskiego 37 Centrum Onkologii w Olsztynie, Oddzial Chemioterapii Olsztyn, NA 10-228, Poland	P04351 Site 46 10 subjects	March 16 to 20, 2015	Preliminary VAI
CI: Luis Fein, M.D. Centro Oncologico de Rosario, Rosario, S2000DSK, Argentina	P04351 Site 9 11 Subjects	January 26 to 30, 2015	Preliminary VAI
CI: Edgardo Salinas, M.D. Hospital Nacional Edgardo Rebagliati Lima, Peru	P04351 Site 38 15 Subjects	January 26 to 30, 2015	VAI
CI: Dariusz Kowalski, M.D. Centrum Onkologii -Instytut im. Marii Sklodowskiej-Curie, ul. W.K. Warszawa, NA 02-781, Poland	TS-P04833 Site 180 63 subjects	March 9 to 13, 2015	Preliminary VAI
CI: Laszlo Mangel, M.D. Medical Center of the University of Pecs, Institute of Oncology/Pecsi Tudomanyegyetem KK, Edesanyak utja 17 Pecs, NA 7624, Hungary	TS-P04833/Site 157 25 Subjects TS-P04834/Site 157 45 Subjects	February 16 to 27, 2015	NAI
CI: Laszlo Urban, M.D. Matrai Gyogyintezet Matrahaza, NA 3233, Hungary	TS-P04834 Site 159 44 Subjects	March 2 to 6, 2015	VAI
CI: Albert Font, M.D. Institut Catala d Oncologia-Hospital Barcelona, NA 8916, Spain	TS-P04833 Site 304 28 Subjects	March 3 to 6, 2015	VAI
CI: Pongsatorn Supaattagorn, M.D. Ubonratchathani Cancer Hospital 405 Klang Ar-Wut Road Muang 34000, Thailand	TS-P04832 Site 409 31 Subjects	February 23 to 27, 2915	VAI
CI: Nashat Y. Gabrail, M.D. 4785 Higbee Avenue NW Canton, OH 44718, USA	TS-P04832/Site 291/ 42 Subjects TS-P04834/Site 291/ 19 Subjects	January 6 to 21, 2015	VAI
Sponsor: Tesaro, Inc. 1000 Winter St., Waltham, MA 02451	Protocols noted above	March 23 to April 1, 2015	Preliminary VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Agnieszka Jagiello-Gruszfeld, M.D. Olsztyn, NA 10-228, Poland**

Note: Observations below for this clinical site inspection are based on e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

a. **What was inspected:** At Site 46 for Protocol P04351, 11 subjects were screened, 10 subjects were enrolled into the double blind phase, and 7 subjects completed Cycle 1. All of the 10 subjects' records were reviewed. The review included informed consent documents, study correspondence, source documents, case report forms, and subject diary data provided to the clinical investigator at the end of the study.

b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events. There were no discrepancies between the data submitted in the NDA and the source data. The following regulatory violations were noted on the Form FDA 483 that was issued at the end of the inspection.
   i. Not following the investigational plan regarding dosing, specifically that dexamethasone and ondansetron were not administered during the 0.5 hour prior to chemotherapy and that telephone contact during days 2-5 was not made for four of the subjects.
   ii. Failure to maintain adequate case histories in regard to expiration dates on investigational product (IP). Specifically, Subject 000111 received expired test article and this was not noted in the case history.

c. **Assessment of data integrity:** The violations cited above appear to be minor and isolated and do not impact data integrity. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Luis Fein, M.D.,
Centro Oncologico de Rosario, Rosario, S2000DSK, Argentina

Note: Observations below for this clinical site inspection are based on e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

a. **What was inspected:** At Site 9 for Protocol P04351, 13 subjects were screened, 11 subjects were enrolled, and 7 subjects completed Cycle 1 of treatment. All informed consent documents were reviewed for all subjects (randomized and screen failures), and source documents for seven subjects were reviewed during the inspection.

b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. There were no discrepancies between the data submitted in the NDA and the source data. A Form FDA 483 was issued because an investigation was not conducted in accordance with the investigational plan. Specifically,
   i. Subject 000100 received SCH 619734/placebo at the same time as he received 5-Fluorouracil during Cycle 1, Day 1 on July 13, 2007. The protocol specifies that SCH619734/placebo should be administered approximately two hours prior to administration of the first chemotherapeutic agent on Day 1.
   ii. Not all site personnel who participated in study P04351 were listed on the Signature of Study Personnel Log, which was used to document the role and responsibilities for the study. For example, four study personnel, three nurses who administered therapeutic agents and study medications, and one laboratory employee who collected blood from study subjects were not listed on the log.
   iii. The time of the administration of SCH 619734/placebo, ondansetron, dexamethasone, and cisplatin were not always documented in the source documents at the time of administration. This occurred for Subject 108 and Subject 605 for Cycle 1.

c. **Assessment of data integrity:** The violations above are considered isolated. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

3. Edgardo Salinas, M.D.
Hospital Nacional Edgardo Rebagliati, Lima, Peru

a. **What was inspected:** At this site, for Protocol P04351, 16 subjects were

screened, 15 subjects were enrolled, and all subjects completed the Cycle 1 of treatment. A total of twelve subjects completed all six chemotherapy cycles. All informed consent documents and source documents were reviewed for all 15 enrolled subjects.

b. **General observations/commentary:** The study was not conducted under IND at this site. There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data. A Form FDA 483 was issued for the following violations:

i. An investigation was not conducted in accordance with the investigational plan. Specifically, Protocol PO4351 defines the requirements for eligibility criteria and study drug and chemotherapy administration:

a. Administer SCH 619734 or placebo approximately 2 hours prior to cisplatin-based chemotherapy". Review of fifteen randomized subjects' records revealed that SCH 619734 was administered prior to cisplatin-based chemotherapy during all visits for 4.5 hours to six subjects (Subjects 000512, 000527, 000538, 000563, 000995 and 000532) and for 7 hours prior to cisplatin-based chemotherapy to four study subjects (Subjects 000533, 00521, 000529 and 000553).

b. The protocol states "Administer ondansetron (32 mg IV) and dexamethasone (20 mg PO) approximately 0.5 hour prior to cisplatin-based chemotherapy." A review of fifteen randomized subjects files revealed that these drugs were administered 5.5 hours prior to cisplatin-based chemotherapy for four study subjects #000533, #000521, #000529, and #000553; and 3 hours prior to cisplatin-based chemotherapy for six study subjects #000512, #000527, #000538, #000563, #000995 and #000532.

<u>Reviewer note:</u> The administration times of these medications are accurately recorded in the data listings for study drug compliance (Listing 16.2.5.1.2). The timing of the administration of test article was to be approximately two hours prior to cisplatin-based chemotherapy. For this protocol, there was no specific definition of cisplatin based therapy and there was no prohibition that taxanes be administered prior to the cisplatin. This is not considered a violation for this protocol.

c. The protocol Lists "Subject has previously received cisplatin" as part of the exclusion criteria. Subject #000538 had "a lot of chemotherapies" as documented by the Clinical Investigator in his notes. However, the chemotherapy infusions received were not specified in the notes.

ii. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically,

a. A review of the Laboratory Requisition Forms utilized for PK sample and Clinically Laboratory sample specimen submissions for the study subjects revealed that on numerous occasions the incorrect forms for designated visits were used. For example, Subject 000538 Cycle 3 Visit 2 samples

collected on June 8, 2007 and Screening Visit samples collected on April 2, 2007 were documented on the VISIT: RETEST form; Subject 000538 Cycle 4 Visit 2 samples collected on July 3, 2007 were documented on Cycle 2 Visit 2 Laboratory Requisition Form.

b. An obliterating fluid, "white-out" was used on the Chemotherapy Log sheet for Subject #000521 dated June 8, 2007 (Cycle 5 Visit 1) to change the Cisplatin-based chemotherapy infusion times and post-hydration infusion time.
c. On June 7, 2007 Cycle III Visit 3, Subject #000533 reported respiratory infection and pharyngitis as documented in his visiting notes; however, only cough was reported for this time period in this subject's corresponding electronic case report form.
d. Serious Adverse reactions based on the laboratory testing were not always reported to the sponsor within 24 hour time period as required by the protocol. For example, the total ANC count for Subject #000527 tested on May 16, 2007 was reported to the sponsor on May 21, 2009.

The following items from the Form FDA 483 are under the observation for lack of protocol adherence, but are considered failure to maintain adequate records:

e. The investigational drug SCH619734/Placebo, dexamethasone, ondansetron, docetaxel, paclitaxel, sodium and potassium chloride, cisplatin-based chemotherapy administration and PK sample collection was to have been documented on the Chemotherapy Log for each cisplatin-based chemotherapy cycle. A review of the Chemotherapy Logs for fifteen randomized study subjects (a total of 80 cycles) from January 10th, 2007 to October 16th, 2007 revealed that he study drug SCH619734/Placebo Kit number that is specific for each study subject was not documented on the Chemotherapy Logs for any of the chemotherapy cycles. There was no documentation that the study drug was received by the person administering it to the study subjects prior to each chemotherapy cycle. A review of the source data revealed that on several occasions the study subjects were scheduled to receive the study drug and cisplatin-based chemotherapy on the same day. For example, three study Subjects #000563, #000564 and #000565 came for Cycle I Visit 1 on June 13, 2007 and had SCH619734/Placebo drug administration at 8:30 am (#000563); at 8:40 am (#000564) and at 9:00 (#000565) as documented on their corresponding Chemotherapy Logs.

<u>Reviewer note:</u> The lack of documentation of administration of test article is of concern; however the impact of this finding is mitigated by the randomized, double-blind nature of the trial.

f. There was no documentation available for review to ensure that the Pharmacokinetic (PK) samples collected three and six hours after the study drug administration were processed within one hour, frozen to -20ºC or below immediately after, and stored at -20ºC or below prior to shipping.

There were no records available for review documenting the shipping of PK samples to the testing laboratory. A review of the testing laboratory reports revealed that samples were stored at the clinical investigator's site from two weeks to at least eight months prior to being shipped to the testing lab. For example, Subject #000553' PK samples were collected on August 29, 2007 and received by the laboratory on April 30, 2008; Subject #000995' PK samples collected on April 10, 2007 were received by the laboratory on August 2, 2007.

iii. Inadequate informed consent, specifically, there was no statement in the informed consent document that noted the possibility that the Food and Drug Administration might inspect the records.

c. **Assessment of data integrity:** The timing of the administration of the medications was accurately captured in the line listings. The lack of documentation of administration of test article is of concern; however the impact of this finding is mitigated by the randomized, double-blind nature of the trial. Although there were numerous violations, overall, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

4. Dariusz Kowalski, M.D.
Klinika Nowotworow Pluca i Klatki Piersiowej, Centrum Onkologii -Instytut im. Marii Sklodowskiej-Curie, ul. W.K. Warszawa, Poland

Note: Observations below for this clinical site inspection are based on e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

a. **What was inspected:** At Site 180 for Protocol TS-P04833, 67 subjects were screened, and 62 subjects were enrolled into the double blind phase and completed the study. Fifteen subjects' records were reviewed. The review included informed consent documents, study correspondence, source documents, case report forms, and subject diary.

b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events. A Form FDA 483 was issued for regulatory violations noted below:

i. Failure to maintain adequate and accurate case histories. Specifically:

a. Subject 3003's (rolapitant) source diary stated "dry heaving" for Day 6, and this is not present in the eCRF.

<u>Reviewer note:</u> "Dry heaves" is in the line listings submitted by the sponsor because this error was detected by the study monitor.

b. Subject 3011's (rolapitant) source diary indicated that the subject took rescue medication on Days 4 and 5, but there is no

documentation that rescue medication (metoclopramide according to the line listings) was dispensed for this subject.

c. Subject 3061(control) the source diary indicated that the subject took rescue medication on Days 2, 3 and 4, but there is no documentation that rescue medication (ondansetron according to the line listings) was dispensed for this subject.

Reviewer note: For this observation, because of the lack of documentation, it cannot be determined exactly whether the medication was taken by the subject and not documented (likely) or that the subject did not take the medication.

d. Subject 3006's (rolapitant) source diary indicated that the subject did not take rescue medication; however, this was indicated as a missing value in the date listings.

ii. Failure to conduct the study in accordance with the investigational plan. Specifically:

a. Four serious adverse events (SAE) were not reported to the sponsor in a timely manner, and one SAE was reported as late as 70 days after the site was notified of the occurrence of the SAE.

b. For three subject diaries, Question 1 was observed to have the date and time written by study personnel.

c. **Assessment of data integrity:** The violations noted including transcription errors and failure to document rescue medication dispensing appear to be non-systematic errors on the part of study staff. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. Laszlo Mangel, M.D.
Medical Center of the University of Pecs, Institute of Oncology, Pecs, Hungary

a. **What was inspected:** At this Site 157 for Protocol TS-P04833, thirty subjects were screened, 25 subjects were enrolled and completed Cycle 1 of the study. Subject records for all 25 subjects were reviewed. The review included informed consent documents, study correspondence, source documents, case report forms, and subject diary data.

For Protocol TS-P04834, fifty subjects were screened, 45 subjects were enrolled and completed Cycle 1 of the study. Subject records for all 25 subjects were reviewed. The review included informed consent documents for 45 subject records, diaries of 28 subject records, and other data points for 23 subject records

b. **General Observations/Commentary:** No significant regulatory violations were noted, and no Form FDA 483 was issued. There was no evidence of under-reporting of adverse events. There were no discrepancies between the data submitted in the NDA and the source data.

c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

6. Laszlo Urban, M.D.
Matrai Gyogyintezet, Matrahaza, NA 3233, Hungary

a. **What was inspected:** At this site, for Protocol TS-P04834, 44 subjects were screened, enrolled and completed the first cycle that contributed to the primary endpoint. The inspection included review of informed consent documents (ICDs), enrollment logs, institutional review board (IRB) correspondence and approvals, sponsor correspondence, investigator agreements (1572s), financial disclosure, adverse event reports, case report forms (CRFs), device accountability records, and source documents.

b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data except for an isolated instance noted below. A Form FDA 483 was issued for inadequate records in that two records were missing: one informed consent form and one randomization sheet (proof of randomization). The CI provided a copy of the randomization sheet in his response of March 18, 2015.

The FDA investigator noted two discrepancies between the line listings and the diary concerning the primary endpoint. Specifically for Subjects 4020 and 4021, both randomized to placebo, the diary on two occasions was left blank for the answer to the question "Did you take any medications for nausea or vomiting over the last 24 hours?" These responses were blank in the diary, but were filled in as "No" on the eCRF, indicating a transcription error on the part of the CI.

c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

7. Albert Font, M.D.
Institut Catala d Oncologia-Hospital Barcelona, NA 8916, Spain

a. **What was inspected:** At this Site 304 for Protocol TS-P04833, 29 subjects were screened, 28 subjects were randomized, and 27 completed Cycle 1 of the study. Subject records for 14 subjects were reviewed. The review included informed consent documents, study correspondence, source documents, case report forms and subject diary data.

b. **General Observations/Commentary:** There were no discrepancies between

the diary data submitted in the NDA and the source data. There was no evidence of under-reporting of adverse events except for the isolated instance noted on the Form FDA 483 below. The Form FDA 483 was issued because:

i. An investigation was not conducted in accordance with the investigational plan. Specifically
   a. For Subjects 3002, 3011, 3015, and 3029, all randomized to active treatment, the order of the dosing plan specified in the Section 7.4.1.3 of the protocol was not always followed in that study drug was not given 1-2 hours before cisplatin or that dexamethasone was not given approximately 30 minutes prior. These violations are contained in the data listings for study drug compliance (Listing 16.2.5.1).
   b. An adverse event of unstable gait for Subject 3020 randomized to control, was not reported in the eCRF.

ii. Failure to maintain adequate case histories. Specifically, the source documents do not contain the subject's life expectancy at the start of the study. Protocol inclusion criteria #4 requires that a subject have a predicted life expectancy of four months or greater.

c. **Assessment of data integrity:** The regulatory violations are isolated. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

8. Pongsatorn Supaattagorn, M.D.
Ubonratchathani Cancer Hospital, Muang 34000, Thailand

a. **What was inspected:** At Site 409 for Protocol TS-P04832, there were 32 subjects screened, 31 subjects were enrolled, and 29 subjects completed Cycle 1 of the study. Subject records for 32 subjects were reviewed. The review included informed consent documents, study correspondence, source documents, case report forms and subject diary data.

b. **General Observations/Commentary:** There were no discrepancies between the diary data submitted in the NDA and the source data. There was no evidence of under-reporting of adverse events. A Form FDA 483 was issued because:

i. An investigation was not conducted in accordance with the investigational plan. Specifically, lack of training may have contributed to Subject 2009 receiving expired medication and the wrong study medication kit.

Reviewer note: This observation was submitted by the sponsor to the NDA in the protocol deviations datasets.

ii. A copy of the written consent form that had been approved by the IRB and signed and dated by the subject was not provided to the subject at the time of consent. Specifically, subjects signed two consent forms. One copy was kept by the CI and the second copy was given to the subject. It was not known whether the two consent forms were identical.

Reviewer note: In his reply of March 17, 2915, Dr. Supaattagorn noted that the two consent forms were identical. He also noted that the site has revised their procedures to provide copies to study participants.

c. **Assessment of data integrity:** The violations are minor and the protocol deviation is contained in the datasets. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

9. Nashat Y. Gabrail, M.D.
4785 Higbee Avenue NW, Canton, OH 44718, USA

a. **What was inspected:** At Site 291 for Protocol TS-P04832, there were 43 subjects screened, 42 subjects were enrolled and completed the first cycle that contributed to the primary endpoint. A total of seven randomized subjects completed all six cycles of the study. Full source data for the first cycle were reviewed for 14 enrolled subjects.

For Protocol TS-P04834, 20 subjects were screened, 19 subjects were enrolled and randomized. Full source data was reviewed for 5 subjects in Protocol 3002. A total of four randomized subjects completed all six cycles of the study. Full source data for the first cycle were reviewed for six enrolled subjects.

The inspection included review of informed consent documents (ICDs), enrollment logs, institutional review board (IRB) correspondence and approvals, sponsor correspondence, investigator agreements (1572s), financial disclosure, adverse event reports, case report forms (CRFs), and source documents.

b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data except for an isolated instance noted below. For Protocol TS-P04832, source records indicated that the subjects appeared to be randomized and dosed with the investigational product in accordance with protocol guidelines with the exception of Subject 2040 who was assigned an incorrect bottle of test article. The sponsor submitted this information to the NDA as a major protocol deviation. A Form FDA 483 was issued for failing to follow the protocol as noted below:

1. Protocol TS-P04832
   a. Three of the 42 randomized subjects (2008, 2025, 2027) did not meet the entrance criteria of the study:
      i. Subject 2008: Prior Cisplatin therapy (reported to the NDA as a deviation).
      ii. Subject 2025: Dosed with Phenothiazine (Phenergan) within 48 hours of study drug (reported to the NDA as a deviation).

iii. Subject 2027 (randomized to placebo): Participated in another clinical study within 30 days of randomization. This deviation is not listed in the NDA submission and there are no documents to show that this issue was reported to the IRB. Subject participated in [redacted] (b) (4) .

b. Four subjects, three assigned active treatment arm and one assigned placebo (Subjects 2008 (placebo), 2011 (active), 2015 (active), and 2025 (active)) were administered Taxanes on Day 1 of dosing cycles prior to cisplatin therapy. Section 7.4.2.1.2 of the protocol required that taxanes be administered on study Day 1 only following cisplatin. The administration times of these medications are accurately recorded in the data listings for study drug compliance (Listing 16.2.5.1).

2. Protocol TS-P04834

a. Documented screening lab results for Subjects 4011 and 4019 indicated that the subjects had a platelet count of 94,000 mm^3 and 91,000 mm^3 respectively. Subjects were required to have platelet counts of > 100,000 mm^3 to be eligible for the study. These are reported as deviations in the NDA submission.

b. Subject 4011 did not complete the Cycle 1 diary; that documented the study's efficacy endpoint. The subject was not dosed with the investigational drug in accordance with protocol guidelines during Cycle 2 of the study. The subject was allowed to continue in the study even though related study procedures were not completed.

The clinical investigator acknowledged the observations and responded to the inspection findings in written communication on February 10, 2015.

c. **Assessment of data integrity:** The violations noted are isolated and not systematic in nature. Except for Observation i(a)(iii) concerning Protocol TS-P04832 (HEC), these observations are contained in the data listings submitted by the sponsor to the NDA. The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

10. Tesaro, Inc.
1000 Winter St., Waltham, MA 02451

Note: Observations below for this sponsor inspection are based on e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

a. **What was inspected:** This inspection evaluated compliance with sponsor responsibilities for the four protocols noted above including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA Form 1572s, and quality assurance (QA). The inspection included review of general correspondence and study master files, site monitoring, and handling

of adverse events and other sponsor/monitor related activities. In addition to the nine study sites noted in the assignment, study files for the following sites were reviewed:

1. Protocol TS-P04833: Site 103 was selected because it was the first site to enroll subjects. Site 181 was selected because this investigator was terminated from the study by the sponsor. The monitor determined that the co-investigator was falsifying records. The IRB and the Polish Ministry of Health were notified. Only two subjects were enrolled in this study at the time. The data was not included in the efficacy analysis; the data was only used in the safety analysis.
2. Protocol TS-P04834: Site 181 – see note above referencing this site. In addition, three sites, (Sites 265, 271, 281) were selected by the FDA investigator because they were managed by U.S. Oncology, a site maintenance organization (SMO) and there was some concern about the oversight by investigators and definition of duties. The monitor for this study was (b) (4)

b. **General Observations/Commentary:** The three Phase 3 protocols were conducted with Tesaro as the sponsor. Protocol P04351, a Phase 2 dose ranging study, was conducted by Schering-Plough from October 2006 to March 2008 at 75 sites in 21 countries prior to Tesaro acquiring the rights to the study. Schering Plough conducted the study in its entirety; Merck purchased Schering and, as a result, the Federal Trade Commission required that Merck divest the IND because they had a similar IND. Overall, the sponsor fulfilled the responsibilities in the conduct of these trials. A Form FDA 483 was issued because the sponsor did not promptly bring clinical investigators into compliance. This occurred specifically for Site 180 for Protocol TS-P04833. The findings at that site are noted above. This also occurred for Site 152 for Protocol TS-P04832 in which the site enrolled 5 subjects and for Protocol TS-P04834 for which the site enrolled 3 subjects.

Schering-Plough followed the procedures in place for conduct of the interim analysis (IA) for Phase 2 studies. However, the adequacy of blinding of the IA for Protocol P04351 was a concern because the actions taken by the sponsor statisticians were not adequately documented in the submission and could not be provided during the inspection. Specifically, confidentiality agreements were missing from the documents submitted to the NDA and the current sponsor was unable to provide them during the inspection. The sponsor provide a notarized statement from the Independent Statistician who conducted the IA stating that the results were not shared with other study personnel.

Reviewer note: At the time of this review, issues of blinding and appropriateness of the statistical analysis preformed for Study P04351 were being reviewed by FDA statisticians. (b) (4)

(b) (4)

c. **Assessment of data integrity:** Except as noted above for the isolated incidences, the monitoring of investigators was adequate and the sponsor maintained adequate oversight of the trials. The three Phase 3 studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications. For Study P04351, the data generated by the clinical sites appears reliable. (b) (4)

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Nine clinical investigator sites and the sponsor were inspected for this application. Data from all clinical sites appears reliable and the sponsor appears to have adequately fulfilled the sponsor responsibilities. Eight of the nine clinical sites and the sponsor have a final or preliminary classification of VAI. Although violations were cited during inspection of three of the investigators for not following the protocol concerning timing of administration of test article and other study medications (Salinas for Protocol P04351, Font for Protocol TS-P04833, and Gabrail for Protocol TS-P04832), the timing of test article administration in relation to other study medications appears to have been accurately captured in the data listings submitted to the NDA, so this data is considered reliable.

Sponsor inspection findings were conveyed to the review division. Because of the concern about the adequacy of documentation of blinding of the IA for Protocol P04351, it is deferred to the statistical and medical review team to determine the adequacy of the IA for Study P04351 to support the indication.

The studies appear to have been conducted adequately, and the data generated by these studies appears acceptable in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Medical Reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Susan D. Thompson, M.D.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN LEIBENHAUT
05/04/2015

SUSAN D THOMPSON
05/04/2015

KASSA AYALEW
05/04/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 29, 2015
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 206500
Product Name and Strength:	Varubi (Rolapitant) Tablets, 90 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Tesaro, Inc.
Submission Date:	September 5, 2014
OSE RCM #:	2014-2148
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Kendra Worthy, Pharm.D.
DMEPA Associate Director:	Lubna Merchant, M.S., Pharm.D.

Reference ID: 3743384

1 REASON FOR REVIEW

This review responds to a request from DGIEP to evaluate the proposed prescribing information, and carton label, for areas of vulnerability that could lead to medication errors. Tesaro Inc. submitted a new molecular entity NDA on September 5, 2014 to DGIEP.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Tesaro Inc. originally proposed a new molecular entity NDA for100 mg rolapitant tablets for prevention of chemotherapy induced nausea and vomiting. On February 12, 2015, DGIEP communicated to the applicant that strength of this drug should be expressed in terms of the active moiety (rolapitant) due to the new USP salt policy. On March 27, 2015, the applicant submitted carton label indicating the new strength (90 mg) for this product. (b) (4)

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(b) (4)

intending to market one package configuration: 2 tablets (b) (4) We note that the dose is 180 mg (2 x 90 mg tablets) prior to initiation of chemotherapy; we find this packaging configuration appropriate. We reviewed the proposed prescribing information and carton label and identified areas that can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide the recommendations in Section 4.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE TESARO INC.

We recommend the following be implemented prior to approval of this NDA:

(b) (4)

2. (b) (4)

3. (b) (4)

4. To ensure that the patients understand both tablets constitute a complete dose and should be taken at the same time, we recommend you revise the

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usual dosage statement from (b) (4) to “ (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Varubi that Tesaro Inc. submitted on September 5, 2014.

Table 2. Relevant Product Information for Varubi	
Initial Approval Date	N/A
Active Ingredient	Rolapitant
Indication	Prevention of chemotherapy induced nausea and vomiting
Route of Administration	Oral
Dosage Form	Tablets
Strength	90 mg
Dose and Frequency	180 mg (2 x 90 mg) 1 to 2 hours prior to initiation of chemotherapy
How Supplied	A single dose package (2 tablets as one set of twinned blisters)
Storage	Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]
Container Closure	Rolapitant 90 mg tablets are packaged in an Aclar blister shell with aluminum foil backing.

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Varubi labels and labeling submitted by Tesaro, Inc. on March 27, 2015.

- Carton labeling

G.2 Label and Labeling Images (next page)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Carton Label Single Dose (180 mg)

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHERLY ABRAHAM
04/29/2015

LUBNA A MERCHANT on behalf of KENDRA C WORTHY
04/30/2015

LUBNA A MERCHANT
04/30/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206500

Application Type: New NDA

Name of Drug/Dosage Form: rolapitant tablets

Applicant: TESARO, Inc.

Receipt Date: September 5, 2014

Goal Date: September 5, 2015

1. Regulatory History and Applicant's Main Proposals

On September 5, 2014, TESARO, Inc. submitted an NDA for rolapitant tablets (referenced IND 72754). The Pre-NDA meeting was held July 2, 2014. Rolapitant is an NK-1 antagonist and an NME. It is the third in its drug class to be submitted to FDA. The proposed indication is the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer rapy. As rolapitant is an NME, it is subject to "the Program" under PDUFA V.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by December 9, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *Sponsor needs to insert product tital above Initial U.S. Approval date*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

NO 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present

Reference ID: 3659912

Selected Requirements of Prescribing Information

• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: *Product Title should be added.*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

NO 10. Product title must be **bolded**.

Comment: *Product title should be added.*

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A

Reference ID: 3659912

15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

    Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

    Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

    Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

    Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

    Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

    Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

    Comment:

Adverse Reactions in Highlights

Reference ID: 3659912

Selected Requirements of Prescribing Information

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

NO 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment: *Sponsor should add the following:"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"*

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Reference ID: 3659912

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

NO 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment: *Section heading must be bolded and should be uppercase.*

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *All subsection headings must be indented and not bolded. The headings should be title case [first letter of all words are capitablized except first letter of prepositions (through), articles (a, an, and the) or conjunctions (for, and)].*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Reference ID: 3659912

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

Reference ID: 3659912

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

NO 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Reference ID: 3659912

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *Sponsor should reference any FDA-approved patient labeling in Section 17. The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).*

NO 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *FDA-aprpoved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17. All FDA-approved patient labeling must appear at the end of the PI upon approval.*

Reference ID: 3659912

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 [text]
  2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 [text]
  5.2 [text]
6 ADVERSE REACTIONS
  6.1 [text]
  6.2 [text]
7 DRUG INTERACTIONS
  7.1 [text]
  7.2 [text]
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Labor and Delivery
  8.3 Nursing Mothers
  8.4 Pediatric Use
  8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
  9.1 Controlled Substance
  9.2 Abuse
  9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.2 Pharmacodynamics
  12.3 Pharmacokinetics
  12.4 Microbiology
  12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
  14.1 [text]
  14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 3659912

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H CHUNG
11/18/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 206500 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: (b) (4) Established/Proper rolapitant Dosage Form: tablets Strengths: 100 mg		
Applicant: Tesaro, Inc. Agent for Applicant (if applicable):		
Date of Application: September 5, 2014 Date of Receipt: September 5, 2014 Date clock started after UN: Not applicable (N/A)		
PDUFA Goal Date: September 4, 2015	Action Goal Date (if different):	
Filing Date: November 4, 2014	Date of Filing Meeting: October 16, 2014	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

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Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 72754	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking***	☒	☐		

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system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☐	☒		

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questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	

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NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☐	☒		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible	☒	☐		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		

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Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* 9/19/14 For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☒	☐	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to*	☒	☐		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm

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approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

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Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	QT IRT: 9/19/14 SEALD: Nov 2014
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

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End-of Phase 2 meeting(s)? **Date(s):** End of Phase 2 CMC Meeting - 1/28/13 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 7/2/14 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** 2/17/2006 ***If yes, distribute letter and/or relevant minutes before filing meeting***	☒	☐		

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ATTACHMENT

MEMO OF FILING MEETING

DATE: October 16, 2014

BACKGROUND: On September 5, 2014, TESARO, Inc. submitted an NDA for rolapitant tablets (referenced IND 72754). The Pre-NDA meeting was held July 2, 2014. Rolapitant is an NK-1 antagonist and an NME. It is the third in its drug class to be submitted to FDA. The proposed indication is the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. As rolapitant is an NME, it is subject to "the Program" under PDUFA V.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mary Chung	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Ruyi He		Y
Division Director/Deputy	Donna Griebel		Y
Office Director/Deputy	Julie Beitz		Y
Clinical	Reviewer:	Aisha Peterson	Y
	TL:	Ruyi He	
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Insook Kim, Jee Eun Lee	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Wen Jen Chen	Y

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	TL:	Mike Welch	Y

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Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tracy Behrsing	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	Y
	TL:	Marie Kowblansky	Y
Biopharmaceutics	Reviewer		
	TL:		
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Sherly Abraham	
	TL:		
OSE/DRISK (REMS)	Reviewer:	Nyedra Booker	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

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Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Alicja Lerner, Katherine Bonson	Y
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	ODE III: Julie Beitz, Maria Walsh		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

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• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: #1 and #4 from left column
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

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Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	None
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

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• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Julie Beitz, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 2/3/2015

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review:

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	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

Reference ID: 3653074

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/s/

MARY H CHUNG
11/04/2014

BRIAN K STRONGIN
11/04/2014

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: October 23, 2014

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Mary Chung, RPM
DGEIP

Subject: QT-IRT Consult to NDA 206500

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated September 19, 2014 regarding the sponsor's labeling submission. The QT-IRT received and reviewed the following materials:

- Your consult
- QT-IRT's previous review regarding study protocol P04852 (under IND 72754, 11/3/2010)
- Proposed label

QT-IRT Comments for DGEIP

The sponsor included the following QT-related language in the proposed label:

12.2. Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2. Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

Thank you for requesting our input into the development of this product under NDA 206500. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

JIANG LIU
10/23/2014

NORMAN L STOCKBRIDGE
10/23/2014